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Risk Assessment in the Federal Government: Managing the Process Working Papers

Committee on the Institutional Means for Assessment of Risks to Public Health, National Research Council

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RISK ASSESSMENT IN THE FEDERAL GOVERNMENT: MANAGING THE PROCESS

WORKING PAPERS

Prepared for:

Committee on the Institutional Means for Assessment of Risks to Public Health
Commission on Life Sciences
NATIONAL RESEARCH COUNCIL

NATIONAL ACADEMY PRESS
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PREFACE

This volume contains papers that were originally prepared for the use of the National Research Council's Committee on the Institutional Means for Assessment of Risks to Public Health. The Committee, in conducting a congressionally mandated study of ways to improve the scientific basis of risk assessment in the federal government, commissioned the work as part of a larger analysis of federal experience. The Committee's final report, Risk Assessment in the Federal Government: Managing the Process, was released in March 1983.

The working papers do not necessarily reflect the judgment or position of the Committee or the National Research Council. They have not been subjected to the internal review procedures that apply to reports prepared by NRC committees.

The three case studies have been reviewed by individuals outside the study project who are directly familiar with the federal analyses and decisions that are described; however, responsibility for them rests with the authors. The purpose of the case studies was to summarize issues raised by others in past decisions on particular substances, but they are not intended to present independent positions or interpretations on scientific or policy matters.

Lawrence E. McCray
Project Director
April 29, 1983

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TABLE OF CONTENTS

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FORMALDEHYDE

The Consumer Product Safety Commission's Risk Assessment for Formaldehyde

William M. Stigliani

A. BACKGROUND AND CONTEXT

1. Describe the chemical and its uses.

Formaldehyde is a colorless, flammable gas with a strong, pungent odor. It can form explosive mixtures with air and oxygen. As an important industrial chemical of major commercial use, formaldehyde is found throughout the environment. In outdoor air, it can originate from many sources such as incinerators, photochemical smog, and engine exhaust. Atmospheric levels of formaldehyde have been reported to range from less than 0.005 ppm to 0.06 ppm near industrial outlets or in areas of heavy smog. Workers who smoke are exposed to additional levels of formaldehyde, since cigarette smoke contains as much as 40 ppm of formaldehyde by volume. Thus, an individual who smokes a pack of cigarettes a day would inhale 0.38 mg, whereas occupational exposure to formaldehyde at 3 ppm could result in a daily intake of 29.0 mg.

Production and Uses

Formaldehyde is usually manufactured by reacting methanol vapor and air over a catalyst (chemical initiator). This results in formaldehyde containing trace amounts of methanol and formic acid. Formaldehyde is sold mainly as an aqueous (water-based) solution called formalin, which is 37% to 50% formaldehyde by

NOTE: This case study describes assessment procedures and summarizes issues and interpretations raised by others, but it is not intended to present independent positions or interpretations on either scientific or policy matters. The case has been reviewed by individuals outside the study project who are directly familiar with the federal analyses and decisions described; however, responsibility for the paper rests with the author, and it does not necessarily reflect the judgment of the Committee on the Institutional Means for Assessment of Risks to Public Health or the National Research Council. It has not been subjected to internal review procedures that apply to reports prepared by NRC committees.

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weight. It is also used in its solid form as paraformaldehyde and s-trioxane. The U.S. produced about 6.4 billion pounds of aqueous formaldehyde in 1978. Most of this quantity was used domestically. The U.S. consumption of formaldehyde by the year 1983 will likely exceed 7.5 billion pounds.

Half of the formaldehyde produced is used to produce synthetic resins such as urea- and phenol-formaldehyde resins. These resins are used primarily as adhesives when making particleboard, fiberboard, and plywood. Urea-formaldehyde concentrates are also used in various coating processes, in paper products, and in making foams for thermal insulation. The textile industry uses formaldehyde for producing creaseproof, crushproof, flame resistant, and shrinkproof fabrics. Acetal resins, made from formaldehyde, are used to mold plastic parts for automobiles, home appliances, hardware, and garden and sporting equipment. Formaldehyde is used in some medicines because it modifies and reduces the toxicity of viruses, venoms, and irritating pollens. The use of formaldehyde in embalming fluids is now required by all state laws.

The widespread use of formaldehyde is due to its high reactivity, colorless nature, purity in commercial form, and low cost. In making other chemicals, it can link similar and dissimilar molecules together. In the paper industry, formaldehyde and its derivatives impart wet strength, as well as shrink and grease resistance. Leather and fur can be tanned by formaldehyde. Formaldehyde is used in the photographic industry because it hardens and insolubilizes the gelatin surfaces of film and papers.

Release of Formaldehyde from Urea-Formaldehyde Foam Insulation (UFFI).

UFFI is a cellular plastic product used as a thermal insulation material. The product is manufactured at the job site by feeding, generally, pressurized air along with two liquid chemicals--a ureaformaldehyde based (or urea-based) resin and a foaming agent-through a foam equipment system. The product that results from this reactive mixture has a shaving cream-like consistency and is usually pumped through relatively small holes into the walls of standing structures. After the UFFI is inside the wall, the insulation becomes firm or self-supporting. Formaldehyde that has not reacted with other chemicals after installation can eventually be released as formaldehyde gas. The likelihood of release of formaldehyde depends on factors such as temperature, humidity, foam formulation, architectural considerations, and installation techniques.

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2. Describe how the question of risk was elevated to the agency agenda*.

Irritation and Sensitization

Initial focus of attention to the possible health problems of UFFI began in October 1976, when the Metropolitan Denver District Attorney's Consumer Office filed a petition, requesting the Consumer Product Safety Commission (CPSC) to develop a safety standard for certain types of home insulation products, including UFFI. The petition claimed that there is an unreasonable risk of injury or irritation associated with UFFI. Over the next three years, several thousand consumer complaints related to irritation and sensitivity from formaldehyde released from UFFI were filed with CPSC.

After considering information compiled by staff, the Commission decided, in March 1979, to defer a decision on the part of the petition relating to UFFI and instructed the staff to evaluate additional information on possible means of addressing the alleged unreasonable risk of injury (44 FR 12080). In addition, in May 1979, CPSC began the sponsorship of a National Academy of Sciences study which examined the acute and sensitization effects due to formaldehyde. The final report, issued in March 1980, stated that "as yet there is no evidence of a population threshold for the irritant effects of formaldehyde in humans." The NAS committee also recommended that levels of formaldehyde be held at the "lowest practical concentration." The latter suggestion may have been influenced to some extent by a preliminary report to CPSC in October 1979 that formaldehyde caused cancer in rats.

In November 1979, staff again briefed the Commission on the status of information gathered concerning formaldehyde toxicity and UFFI. Follow-up investigation of some of the reported complaints indicated a range of severity of reported reactions varying from short-term discomfort to alleged chronic impairment, such as loss of visual acuity, reduction in lung function, and sensitization to other sources of formaldehyde.

As a results of these briefings, the Commission decided to hold public hearings to obtain additional information on safety and health problems associated with UFFI (44 FR 69578). The Commission held public hearings in Portland, Oregon; Atlanta, Georgia; Minneapolis, Minnesota; and Hartford, Connecticut from December 1979, through February 1980. Consumers, industry representatives, state and local government officials, scientists, and others testified at the hearings as to their experiences with UFFI and formaldehyde. Based on the information obtained in these hearings as well as the consumer complaints and medical and

* This case study describes activities only through April 1982.

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scientific information obtained beforehand, the Commission, on June 10, 1980, proposed a rule requiring manufacturers of UFFI to give specified performance and technical information to purchasers to alert them about the possible adverse health effects associated with the release of formaldehyde gas from the product after it is installed in residences (45 FR 39434).

Carcinogenic Risk

In October 1979, representatives of the Formaldehyde Institute, an industry trade association, reported to CPSC the preliminary findings from a carcinogenicity study sponsored by the Chemical Industry Institute for Toxicology (CIIT). This study showed that rats exposed to 15 ppm of formaldehyde developed squamous cell carcinoma of the nose.

In January 1980, an Interagency Regulatory Liaison Group (IRLG) task force including six pathologists visited CIIT to obtain additional information concerning the long-term study and to verify the findings. In a report prepared in February 1980, the group concurred, in general, with the CIIT observations, diagnoses, and interpretations.

As the CIIT experiment progressed and more data became available, the need for a full review of the potential health risks of cancer and other genetic diseases to humans from chronic exposure to formaldehyde became evident. In April 1980, CPSC, in conjunction with the National Toxicology Program (NTP) formed the Formaldehyde Panel, consisting of 16 federal scientists, charged with reviewing and evaluating the available published and un-published information, including the ongoing CIIT study. In its final report to CPSC in November 1980, the panel concluded that it would be "prudent to regard formaldehyde as posing a carcinogenic risk to humans."

Based in part on the findings of the Formaldehyde Panel, as well as on its determination of the irritating and sensitizing effects of formaldehyde, CPSC called for a proposed ban of UFFI in February 1981. The rule was made final in April 1982.

3. Under what statutes and agency jurisdiction does the chemical fall? What statutory tests governed the decision?

The ban of UFFI falls under the jurisdiction of two possible CPSC statutes. These are: Section 8 of the Consumer Product Safety Act (CPSA) and Section 2(q)(1)(B) of the Federal Hazardous Substances Act (FHSA). The Commission chose to regulate under the CPSA for two reasons. First, under the FHSA, the Commission lacked the authority to cover products installed in nonresidential applications such as schools. Secondly, because of the complex and lengthy nature of the rulemaking proceeding that would be required under the FHSA, the Commission believed it would be in the public interest to regulate this product under the CPSA.

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Under Section 8 of the CPSA, there are two criteria that must be met before the Commission can issue a proposed ban. These are:

(1) The consumer product is being, or will be, distributed in commerce and presents an unreasonable risk of injury; and
(2) No feasible standard under the Act, including requirements for warnings and instructions, would adequately protect the public from the unreasonable risk of injury associated with the product.

In CPSC's judgment, unreasonable risk was demonstrated by the irritant and sensitizing effects, and carcinogenic potential of formaldehyde. The Commission examined the existing information concerning the feasibility of a standard and found that there was no feasible standard, including labeling, that would adequately protect the public.

In its finding that it was not possible to establish a feasibility standard, CPSC denied a petition it received from the Formaldehyde Institute on April 16, 1981, which requested that the Commission issue a safety standard applicable to UFFI.

4. What was the decision schedule? Note any statutory or other action deadlines.

October 1976

Action: The Metropolitan Denver District Attorney's Consumer Office filed a petition to CPSC, requesting the Commission to develop a safety standard for insulation products, including U.F.F.I.

June 10, 1980

Action: CPSC issued a proposed rule to require manufacturers of UFFI to give information to prospective purchasers to alert them to the possible adverse health effects associated with the release of formaldehyde gas from the product.

Deadlines: Written comments to proposed rule to be submitted by August 11, 1980.

Compliance to begin six weeks after publication of final rule.

November 20, 1980

Submission of Formaldehyde Panel report to CPSC.

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February 5, 1981

Action: CPSC issues a proposed rule to ban UFFI from residential, commercial, and public buildings in the U.S.

CPSC denies the Denver petition of October 1976.

Deadlines: Written comments to proposed rule to be submitted by April 6, 1981.

Oral presentation by interested parties concerning proposed rule to be presented March 20, 1981.

April 10, 1981

Action: The Formaldehyde Institute filed a petition to CPSC, requesting that the Commission issue a safety standard applicable to UFFI.

October 26, 1981

Completion of CPSC's quantitative risk assessment.

April 2, 1982

Action: CPSC issues a rule to ban UFFI from residences and schools in the U.S.

CPSC withdraws proposed rule of June 10, 1980.

CPSC denies Formaldehyde Institute petition of April 10, 1981.

Deadlines: The ban is effective on or after August 10, 1982 or the day after the expiration of the 90 calendar day period of continuing session of Congress following promulgation of the ban, whichever date is later.

B. IDENTIFICATION OF HAZARD (determining the presence or absence of potential toxic effects)

1. What health endpoints were evaluated?

CPSC evaluated a wide range of potential adverse health effects from formaldehyde exposure. Acute effects, such as irritation of the eyes, nose and respiratory tract were examined, as well as a wide variety of other effects such as drowsiness, nausea and headaches.

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Sensitization of certain individuals due to formaldehye exposure was also addressed. CPSC was concerned about a small segment of the population which could be susceptible to severe reactions such as allergic dermititis and asthma.

Finally, CPSC reviewed the potential of formaldehyde to induce genetic disease. Its effects on reproduction and teratogenicity, mutagenicity and carcinogenicity were reviewed and evaluated, although the main focus was on cancer.

2. What were the key data available for review? (What additional data were sought?)

Prior to the release of preliminary data from the CIIT study in November 1979, CPSC was almost exclusively concerned with potential acute effects and hypersensitivity caused by formaldehyde exposure. Over the course of about three years, the Commission had received over 2,000 consumer complaints of adverse health effects from the release of formaldehyde gas from UFFI. These complaints provided the CPSC with a readily available data base to examine the effects of interest. The Commission staff conducted follow-up investigations for over 200 of the complaints.

In addition, CPSC asked the National Academy of Sciences (NAS) to conduct a study assessing the health effects of formaldehyde. A final report to the Commission was completed in March 1980. Two other NAS studies Indoor Pollutants (1981) and Formaldehyde and Other Aldehydes (1981) were available for review and evaluation.

After November 1979, CPSC was also concerned with the potential carcinogenic effect of formaldehyde. Review of the CIIT rat study began while it was still in progress. In January 1980, an IRLG task force was formed to verify the initial findings of CIIT and to seek further information. In a report prepared in February 1980, the group concurred in general with the CIIT observations. In April 1980, CPSC, in conjunction with the National Toxicology Program (NTP) formed the Formaldehyde Panel, consisting of 16 federal scientists, to continue the review of the ongoing CIIT study. In addition, the Panel was charged with evaluating all available published and nonpublished literature relating to other genotoxic endpoints. In November 1980, the Panel reported its conclusion to CPSC that it is prudent to regard formaldehyde as a human carcinogen.

Four other groups of scientists in separate reports endorsed the opinion that formaldehyde should be viewed as if it were a human carcinogen. The first was a NIOSH Current Intelligence Bulletin. Another was a report based on a rat study conducted by scientists at New York University. In a letter sent to CPSC by Dr. A. Upton, professor and chairman of the New York University Medical Center, the NYU study was cited as providing “decisive confirmation of the CIIT findings.” The third was a report from a

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working group of the International Agency for Research on Cancer (IARC) in October 1981. A fourth group, in a report to the American Cancer Society by the Environmental Cancer Information Unit, chaired by I. J. Selikoff and E. C. Hammond (February 1981), found that formaldehyde was an animal carcinogen and that human exposures should be reduced or eliminated.

There were some limited human studies on industry workers and morticians. CPSC found these to be inconclusive regarding their ability to predict human carcinogenic effects. The same conclusion was drawn by a working group of IARC.

3. Who performed the initial analysis? (What was their background? Available analytic resources?)

Irritation and Sensitivity

From the thousands of consumer complaints CPSC received, several hundred were singled out for follow-up investigation by CPSC. Part of the investigation consisted of answering a questionnaire. Questions were designed by staff epidemiologists and chemists. In addition, when the complainant was treated by a physician, the doctor was contacted to obtain further details. Also, a medical officer on the CPSC staff reviewed the complaint file.

The NAS analysis of health effects of formaldehyde, which was a key document in CPSC's assessment of acute symptoms, was performed by 13 medical doctors and scientists. They had expertise in various areas including toxicology, epidemiology, and dermatology.

Carcinogenic Effects

The IRLG task force that made the preliminary evaluation of the CIIT study in January 1980 consisted of six pathologists representing CPSC, NIEHS, DOE, EPA and NCI as well as other health scientists. The Formaldehyde Panel which made the final evaluation of the CIIT study for CPSC consisted of sixteen scientists from various federal agencies including EPA, DOE, NCI, FDA, NIEHS, NIOSH, NCTR, and OSHA. All of these had Ph.D.s, Sc.D.s or M.D.s, and they represented expertise in the areas of carcinogenicity, metabolism, teratology and reproduction, epidemiology, mutagenicity, and risk analysis.

The CPSC staff reviewing the formaldehyde data in both of these areas consisted of six Ph.D.s or D.V.M.s. They had backgrounds in carcinogenicity, metabolism, mutagenicity, risk analysis and toxicology, biochemistry and pathology.

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4. How was uncertainty described in reaching final interpretations? Were crucial assumptions made explicit?

Irritation and Sensitivity

The identification of the effects of irritation and hyper-sensitivity caused by formaldehyde exposure is quite certain. Controlled human studies where small numbers of young healthy adults were exposed to concentrations of formaldehyde varying from 20 ppm to less than 1 ppm for short periods provide the best evidence. The NAS study on health effects of formaldehyde (March 1980) discusses these and other relevant evidence in detail.

There is some question as to whether studies on limited populations are applicable to the general population. The NAS study notes this limitation and enumerates the factors that might lead to a wide range of individual susceptibility; e.g., health status, genetic predisposition, age, pregnancy. Notwithstanding these factors, the NAS report does caution that "responses reported in controlled studies may occur at an increased rate in the general population, because of the interaction between formaldehyde and other irritants in the environment." Finally, NAS states: "Some of the factors might decrease susceptibility; most may increase it."

The possible existence of a threshold to irritation and hypersensitivity raises another point of uncertainty. The NAS study states, "As yet, there is no evidence of a population threshold for the irritant effects of formaldehyde in humans." The NAS leaves this question unresolved but advised maintaining "formaldehyde at the lowest practical concentration to minimize adverse effects on public health." By the time NAS committee members wrote the final report, the preliminary results of the CIIT study were known. This new information probably affected their final recommendations.

Carcinogenicity

Since there are no definitive human studies to date for carcinogenic effects of formaldehyde, its potential carcinogenicity in humans must be inferred from animal data. The lack of direct evidence was clearly stated by the Formaldehyde Panel. The Panel concluded that "definitive experiments exist which demonstrate the mutagenicity and carcinogenicity of formaldehyde under laboratory conditions." It further stated that "the data presently available do not permit a direct assessment of the carcinogenicity of formaldehyde to man." In reaching its final determination it stated: "it is the conclusion of the Panel that it is prudent to regard formaldehyde as posing a carcinogenic risk to humans."

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5. What qualitative factors affected the weighting of data?

There were two particular features of the CIIT study which the Formaldehyde Panel weighed before reaching its conclusions. One was the occurrence of a viral upper respiratory tract infection (sialodacyoadenitis) in the test animals at twelve months of exposure that lasted about one week. The virus event left open the possibility that the infection served as a co-carcinogenic effect contributing to the carcinoma response.

The other feature was that the rats developed severe irritation in their nasal cavities due to formaldehyde exposure. This symptom raised the question of whether irritation effects in and of themselves could cause or contribute to a carcinogenic response.

The Formaldehyde Panel, in considering these two questions, did not completely discount their importance, but concluded that it was unlikely that either could cause an experimental artifact. With regard to the viral infection, the Panel report stated that "nasal tumors had probably already formed at the time of the infection," thus casting doubt upon the possibility of a co-carcinogenic response.

The Panel addressed the question of irritation by stating they "found no evidence that the induction of irritation ... is a sufficient condition for the carcinogenic activity of an agent."

6. What inference options were used in the Hazard Identification step? Were they explicit and in accord with any general guidelines?

Inference Options Used in Hazard Identification*

(1) Degree of confirmation of positive results; significance of negative results: The Formaldehyde Panel reached its conclusion based on the positive CIIT rat study as well as other supporting evidence. This evidence included:

(a) The NYU rat study of Laskin et al. that demonstrated a positive carcinogenic response from a different strain.
(b) The demonstrated genotoxicity of formaldehyde.

* The inference options cited here are drawn from Risk Assessment in the Federal Government: Managing the Process, NAS (1983), pp. 29-30.

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(c) Suggestive evidence from species other than the rat and tissues other than the nasal epithelium; e.g., lesions interpreted to be carcinomas in situ induced in the oral mucosa of rabbits.

The Panel reviewed the known data for hamsters, which apparently did not exhibit a carcinogenic response to formaldehyde. This negative result did not appear to influence the Panel's final conclusion, based on the positive animal studies.**

(2) Evidence of different metabolic pathways between animals and humans: The Formaldehyde Panel reviewed extensively the known data about formaldehyde metabolism but did not reach any conclusions about interspecies difference. The Panel did recommend as future research, that "the pharmacokinetics of formaldehyde and its interaction with target tissue should be studied in several animal species."

(3) Findings of tissue damage and other effects in the interpretation of tumor data: The Formaldehyde Panel considered both the irritation effects and the cytotoxic affects of formaldehyde. For irritation the Panel concluded that it was "conceivable that the 'irritant' effect of formaldehyde...may contribute to some extent to the expression of its carcinogenic activity through a mechanism enhancing the promoting or tumor growth stage of carcinogenesis. However, it must be added that our knowledge of this type of effect is still quite inadequate and not directly applicable to the reported carcinogenic effects of formaldehyde on the nasal mucosa."

Regarding cytotoxicity, the Panel noted that "most carcinogens have significant cytotoxic effects. Therefore, formaldehyde is not an unusual case....In short, it is conceivable that the cytotoxic effects of formaldehyde may play a part of its overall carcinogenicity."

(4) Use of short-term test data: As noted above, the Formaldehyde Panel used short-term tests demonstrating the genotoxic effects of formaldehyde as supportive evidence for the carcinogenic effects of formaldehyde.

** The Panel did cite a (as yet unpublished) report indicating that formaldehyde might act as a tumor "enhancing agent" in the trachea of hamsters, but acknowledged the study was limited.

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Explicitness and Accordance with General Guidelines

All of the inference options cited above were quite explicit in the Formaldehyde Panel report. Accordance of these inference options with general guidelines can be described as follows.

(1) Degree of confirmation of positive results; significance of negative results: The degree of confirmation used by the Formaldehyde Panel in reaching its conclusions appears to be in agreement with past guidelines of federal agencies: CPSC (1978), IRLG (1979), OSHA (1980).* These generally state that positive evidence in one or more animal species is sufficient to treat a chemical as if it were a human carcinogen. Most of these also state that negative results in animals should not supersede positive results and that short-term tests should serve as supportive, but not conclusive evidence. The guidelines for the International Agency for Research on Cancer (IARC) deal exclusively with hazard identification and are currently in use. It appears that the Formaldehyde Panel's use of positive animal and short-term tests is in accord with the IARC guidelines as well. Under the IARC classification system, sufficient evidence of carcinogenicity in animals** exists if there is an increased incidence of malignant tumors:

(a) in multiple species or strains; or
(b) in multiple experiments; or
(c) to an unusual degree with regard to incidence, site or type of tumor, or age at onset. Additional evidence may be provided by data on dose-response effects, as well as information from short-term tests or on chemical structure.

* Some reviewers of a draft of this case study questioned the relevance and appropriateness of citing past agency guidelines. While it is true that most of these are no longer in use (and no new ones have come forth recently) due to a variety of complex policy and scientific reasons, the author of this case study feels it is nevertheless instructive to indicate accordance with previous guidelines. This does not imply that CPSC or the Formaldehyde Panel utilized the guidelines cited (in fact no reference to guidelines is listed in their reports). It does imply that there is some historical precedent within the federal agencies for the choices of inference options which the Formaldehyde Panel and CPSC applied to their risk assessments.

** A determination of “sufficient evidence” in animals categorizes a chemical as as a “probable” human carcinogen in the IARC scheme.

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(2) Evidence of different metabolic pathways between animals and humans: The Formaldehyde Panel made no conclusive statement on this component due to lack of evidence. Past agency guidelines (e.g., OSHA, ; IRLG) have acknowledged the importance of metabolic differences between species, but also have noted that normally evidence is not adequate to incorporate such information.

(3) Findings of tissue damage and other effects in the interpretation of tumor data: The author of this case study has found no specific reference in guidelines dealing with tissue damage and other toxic effects.

(4) Use of short-term test data: The Formaldehyde Panel's use of short-term test data as supportive evidence for carcinogenicity appears to be in accord with most guidelines which have addressed this component.

7. Describe any internal, internal-advisory (e.g., EPA's SAB) and external (e.g., NAS) scientific review of the initial analysis. What, if any, criticism was incurred?

There was no scientific review of the Formaldehyde Panel's report.

8. How were issues raised in the review(s) accommodated?

This question is not applicable.

9. What other issues arose concerning scientific data and their use? Briefly describe dissenting opinion (as pertaining to hazard identification only).

In response to the proposal to ban UFFI, CPSC received hundreds of written comments and 21 oral presentations. Included among the commenters were industry representatives, consumers, consumer organizations, consultants, scientists, and federal, state and local government agencies. The major points raised are summarized as follows:

Irritation and Sensitization

The relationship of reported symptoms to UFFI was challenged. Commenters noted that complaints to CPSC from consumers living in UFFI homes did not constitute a causal relationship between symptoms and formaldehyde exposure. Some commenters stated that there was a failure of the complaint data to demonstrate a dose-response relationship. Others argued that the absence of formaldehyde measurement data in some of the complaint reports weakened the alleged causal relationship.

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Some commenters contended that levels of formaldehyde found in UFFI homes were too low to cause the reported effects. Exposure studies on human volunteers, which have demonstrated adverse health effects to at least as low as 0.2 ppm, were attacked. Criticism of experimental conditions (alleged crowding, temperature, and humidity), the lack of a dose-response relationship, and the lack of appropriate control groups in these studies were cited.

Some commenters stated that there was evidence showing there to be no difference in formaldehyde levels between homes with and without UFFI. This contention was based on a recent University of Iowa study, although apparently no detailed data in support of this finding was presented at the time.

In the opinion of another commenter, studies showed that there was no difference in formaldehyde levels between "properly foamed" homes and homes without UFFI.

Carcinogenicity

Some commenters stated that the CIIT rat study is flawed because formaldehyde exposure at 15 ppm caused ulceration and acute exudative inflammation, which are in themselves cancer inducing. Others asserted that the viral epidemic in the rats of the CIIT study invalidated the results. These questions had been considered earlier by the Formaldehyde Panel (see Question B.5).

A number of commenters argued that there were studies showing that persons occupationally exposed to formaldehyde did not develop cancer at higher than normal rates. Epidemiologic studies on formaldehyde industry workers and morticians were cited. CPSC considered the results to be inconclusive rather than demonstrating that formaldehyde is not carcinogenic in humans.

Other commenters noted that there appears to be a wide interspecies variation of response to formaldehyde. Hamsters do not appear to exhibit a carcinogenic response, mice exhibit a relatively low response, while rats show a large response (at 15 ppm). In the view of these commenters, judgment about the carcinogenic effect of formaldehyde in humans should be tempered by the fact of wide interspecies variation of response in animals.

10. Is the substance subject to past or possible future regulatory actions in other programs? If so, did the program office coordinate with other agencies or programs?

Formaldehyde is subject to possible future regulatory actions by EPA and OSHA. In addition, HUD is considering rulemaking for UFFI in mobile homes. DOE has stated that its proposed UFFI regulations would conform with any legal actions taken by CPSC. FDA has the mandate to regulate but no serious action has been taken thus far based on the agency decision that no uses for which it has jurisdiction lead to direct nasal exposure or inhalation exposure in humans.

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Initially, there was considerable coordination of agency programs under the Interagency Regulatory Liaison Group (IRLG). In the spring of 1980, the IRLG had chosen formaldehyde as one of 6 Category I substances. The specific intent of such a classification was to ensure that the selected chemical would receive focused attention for the purpose of integrating regulatory programs due to the imminency of regulation by one or more of the agencies. A Formaldehyde Task Group was assigned to accomplish this goal, and a detailed Regulatory Development Workplan, including a timetable for action, was prepared.

One activity of the Task Group was to examine the feasibility of developing an integrated, interagency risk assessment for formaldehyde. The ultimate goal of the coordinated risk assessment was to develop a single document which could be utilized by the IRLG agencies as baseline information for regulatory action. This effort was only the second attempt of the federal government at a unified approach to risk assessment. (A similar effort for chlorofluorocarbons was already in progress at the time.)

CPSC took the lead in developing a quantitative risk assessment which was reviewed and approved by other IRLG agencies. IRLG hired a contractor to prepare and compile all the exposure data that was available for all possible areas of interest; i.e., occupational, drug related, environmental, and consumer. The idea was to apply the risk assessment to that information in order to estimate where the greatest number at risk might be, so that priorities could be set across agencies. The contract was not completed before IRLG was disbanded in September 1981.

Although CPSC, EPA, OSHA, and HUD signed a Statement of Policy Coordination regarding potential regulatory control of formaldehyde in the spring of 1981, there has been an apparent reversal of the effort to coordinate regulation even previous to the official expiration date of IRLG. This change in trend is highlighted by the different and, in some ways, contradictory approaches toward regulating formaldehyde taken by CPSC and EPA in 1981-82. (See also Question D.2. for detailed analysis.)

C. QUANTIFICATION AND CHARACTERIZATION OF RISK TO HUMANS

(This section deals with CPSC's quantitative risk assessment of October 26, 1981. Acute effects, mutagens and other possible hazards will not be dealt with since these have not been quantified.)

1. What health points were evaluated?

Malignant cancer was the only health endpoint evaluated. The risk assessment did not specify any particular target organs in humans.

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2. What were the key data available for review? (What additional data were sought?)

Animal Data

The risk assessment utilized data exclusively from the CIIT rat study.

Human Exposure

There were two types of human exposure data. One type was obtained from actual on-site measurement of UFFI and non-UFFI residences. The other type was obtained from controlled laboratory studies using UFFI panels, formed under conditions of best available technology by manufacturer's representatives.

The on-site measurements consisted of 827 data points from UFFI residences in which an adverse health effect was reported (“complaint” homes) and 337 data points from UFFI residences in which no complaints were reported. Since formaldehyde levels in “complaint” and “noncomplaint” UFFI residences did not significantly differ from one another, all 1164 data points were used to estimate an average age-of-foam related formaldehyde level. One hundred three data points were also obtained from non-UFFI residences. This data was used to subtract out a background level of formaldehyde in residences. Sources of data came from “in-depth” CPSC studies, numerous reports from ten states and Canada, as well as studies sponsored by various universities and the Formaldehyde Institute.

Originally, CPSC utilized on-site data for “complaint” homes only. The laboratory studies of UFFI panels were used by CPSC to assess the exposure for the total population, including UFFI residences where no complaints were reported. When further on-site data analysis showed no significant difference in exposure levels for “complaint” and “noncomplaint” homes, the lab studies were continued so that risk could be calculated using another data base.

The lab studies consisted of estimating the average projected formaldehyde level in a hypothetical corner room for each of 24 panels foamed by manufacturers' representatives under optimum conditions. The Franklin Institute Research Laboratories (FIRL) performed the initial study under contract from CPSC. Oak Ridge National Laboratory (ORNL) did a follow-up study also sponsored by CPSC. CPSC engineering staff worked closely with ORNL to develop a recommended analytic methodology.

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3. Who performed the initial analysis? (What was their background? Available analytic resources?)

A CPSC staff member with a B.S. in analytic chemistry and 20 years of experience was the main person responsible for verifying the data for on-site exposure measurements obtained from the various sources mentioned in Question C.2. Verification consisted of reviewing the testing methodology to determine its acceptability.

Engineers from FIRL, ORNL, and CPSC designed the laboratory studies on exposure from the formaldehyde panels.

The quantitative assessment of the dose-response curve was originally determined by a Ph.D. risk expert from the National Center for Toxicological Research as part of the Formaldehyde Panel report. A CPSC staff person with a Ph.D. in biochemistry and two years of experience in risk assessment did an independent analysis for CPSC. (Section C deals entirely with the latter analysis.)

A complete set of computer programs for dose-response and statistical analysis were available to CPSC staff.

4. To what extent were results presented quantitatively? What factors influenced the degree of quantification?

The results were presented in a precisely quantitative manner, as chances per million of developing malignant cancer during a lifetime. Three different estimates were given. Two of the estimates were based on the linearized multistage model of Crump, et al. (1979). They were obtained by applying the model to the two different exposure data bases described in Question C.2. The third estimate, which predicts essentially zero risk, is based on the "best-fit-of-data" model which is a purely statistical fit of a polynomial curve to the data.

The factors that influenced the degree of quantification were: (1) a well conducted rat study, showing a pronounced dose-response effect, which incorporated three different doses, plus a control and consisted of 120 animals per sex per species per dose level and (2) exposure data from two independent data bases; one of which contained over 1000 data points.

5. How was uncertainty described in reaching final interpretations? Were crucial assumptions made explicit?

Generally, in predicting human risk from animal data, there are two areas of great uncertainty. These are: (1) the extrapolation to low dose of risk observable at much larger doses and (2) transferring the risk from animals to humans (interspecies conversion).

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The CPSC risk assessment dealt with uncertainty in extrapolation by presenting the risk from two different dose-response curves which, most plausibly, define the upper and lower limits of risk. The upper estimate was based on a linerized multistage model (95% upper confidence limit (UCL)), which is usually considered to be a conservative estimate. The lower estimate, based on a "best-fit-of-data" model, minimizes the risk. Assumptions for using these models are clearly delineated. (See Questions C.6 and C.7 for details.)

The uncertainty in choosing an interspecies conversion factor was not accounted for in the CPSC risk assessment. Only one conversion factor was utilized. The risk to rats for a given concentration in air was assumed to cause the same risk to humans at that concentration. The rationale for this premise was a paper by Mantel and Schneiderman (1975). Furthermore, the duration of exposure in rats was corrected for humans by calculating duration as a proportion of species lifetime. Although these assumptions may be reasonable, Mantel and Schneiderman describe them as first order approximations. It is not clear whether the selected conversion factor is conservative or liberal with respect to other conversion factors that could have been used.

In addition, there was no statement about the pharmacokinetics of formaldehyde in rats and humans and whether or not there were any features that might cause differences in response between the two species. It is quite likely that such information was lacking or unavailable, but CPSC did not state so.

6. How were qualitative factors dealt with?

- Mechanisms of action, associated thresholds
- Effects on population subgroups
- Other confounding factors

Mechanisms of Action

The risk assessment states that the most likely mechanism of action of formaldehyde is its ability to interact "with ongoing processes in the human body which can lead to cancer, and potential interaction with other carcinogens that humans may be exposed to." CPSC supports this assertion by citing formaldehyde's ability to interact with the genetic material (DNA) in a wide variety of short-term tests. Given these mechanisms, CPSC asserts that linearity of the dose-response curve at low exposure levels is most applicable.

CPSC considers the "unlikely" event that formaldehyde might not interact with an ongoing chemical process. In that case, the "best-fit-of-data" estimate (with essentially zero risk at low dose) is asserted to be the most applicable.

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Effects of population subgroups: There is no discussion of this topic in the risk assessment.

Other confounding factors: CPSC depended entirely on CIIT for the release of tumor data. CPSC staff had to make certain assumptions regarding the data that probably would not have been necessary had the experiment been under their control. Some of these assumptions were as follows:

(1) Rats developing tumors early on were assumed to have received a 24-month exposure to formaldehyde;
(2) Data on the rats was available only through 24 months of age; the analysis does not compensate for the fact that, had they been allowed to live, more rats would likely have developed cancer;
(3) CIIT made scheduled serial sacrifices of rats at 6, 12, and 18 months. CPSC omitted all data on animals sacrificed early since these would not have had the same opportunity to develop a tumor as they would had they been allowed to survive for longer periods. Eight animals (out of 40) sacrificed at 18 months had malignant tumors at the high dose. This data was omitted; and
(4) Although there was a significant incidence of benign tumors in the test animals, CIIT declined to release the data on the ground that no dose-response relationship was observed. CPSC, therefore, did not consider benign tumors in its assessment.

7. What qualitative factors affected the weighting of data?

The major qualitative factor that affected the weighting of data was the consideration of biologic plausibility in the choice of a dose-response model. Both the Formaldehyde Panel and CPSC strongly endorsed the use of the linearized multistage model. This preference was based on their belief that it is the most consistent with prevalent theories on chemical carcinogenesis. (See Question C.6.)

Another qualitative factor which may have affected the final results was the omission of data on benign tumors. This omission was not decided on the basis of policy but, rather, because the data was not available from CIIT. Since there was no detailed discussion of the significance of benign tumor data in the risk assessment, it is difficult to determine how the data would have been interpreted and incorporated into the final results.

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8. What inference options were used in the quantification of risk? Were they explicit and in accord with any general guidelines?

Inference Options Used in Dose-Response Assessment*

(1) Choice of extrapolation models: CPSC chose a modified multistage model which incorporates linearity at low exposure levels (the linearized multistage model). CPSC also calculated risk based on a purely statistical fit of the multistage model, making no provision to take linearity into account at low dose. CPSC's risk assessment explicitly endorses the linearized model over the latter model.

(2) Choice of confidence limits or best estimates: The linearized multistage model utilized the 95% upper confidence limit. The purely statistical model utilized "maximum likelihood estimates."

(3) Choice of interspecies conversion factor: CPSC assumed that the risk to rats at a particular concentration was equal to the risk to humans at the same concentration, and that the duration of risk should be based on the proportion of lifetime for a given species.

(4) Use of information comparing differences in metabolic processes and rates in experimental animals and humans: CPSC did not discuss this component, finding that information regarding it was inadequate or lacking. CPSC implicitly assumed similarity of processes and rates between rats and humans.

(5) Treatment of data when data from more than one species or strain is available: Data from CIIT were available for two species, the rat and the mouse. The CPSC quantitative risk assessment utilized data from the rat study only. The rat is considerably more sensitive to formaldehyde than any other species tested to date.

Explicitness and Accordance with General Guidelines

The first three inference options were explicitly stated in the CPSC risk assessment, while the latter two were not explicitly stated.

Accordance of CPSC's selected inference options with general guidelines can be described as follows:

* The inference options cited here are drawn from Risk Assessment in the Federal Government, Managing the Process, NAS (1983), pp. 31-32.

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(1) Choice of extrapolation models: The use of a linearized model was in accord with most guidelines developed by federal agencies in the past. The linearized multistage model, a sophisticated type of linear model, had been adopted by EPA's Carcinogen Assessment Groups (CAG) in the summer of 1980. The use of a less sophisticated linear model had been advocated earlier by senior EPA officials (EPA, 1977), although they also stated "the use of several extrapolation models is appropriate to convey the range of uncertainty in these elements." FDA endorsed the use of the linear model in its proposed guidelines regarding chemical compounds in food-producing animals (FDA, 1979). The IRLG guidelines (IRLG, 1979) stated that linear extrapolation "should always be included among any methods."

The use of a linearized model for dose-response assessment has not been universally accepted as a general guideline. Some have argued that for particular chemicals, other models may provide a better fit, or that linear extrapolation may only apply when the chemical in question is genotoxic. For example, the Food Safety Council, a trade association, has stated:

1. Where the linear (one-hit) model fits the dose-response and biochemical data in the observed range as well as other models, it should be used.
2. If the toxicity in question is a genotoxic carcinogen, then the one-hit (low-dose linear) model is appropriate.
3. If the two cases above do not apply and the one-hit model clearly does not fit the data, then the better-fitting model should be chosen. It should be applied with whatever conservatism seems appropriate from the data. Such conservatism is particularly appropriate when the substance is genotoxic.

(2) Choice of confidence limits or best estimates: The use of the 95% upper confidence limit was in accord with the procedure of EPA's Carcinogen Assessment Group. The use of "maximum likelihood estimate" has not been explicitly endorsed in any federal agency guidelines to the knowledge of the author of this report. An OSTP report in 1979, did however, endorse the use of "most likely value" in estimating risk quantitatively (OSTP, 1979).

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(3) Choice of interspecies conversion factor: The choice of conversion factor was based on a paper by Mantel and Schneiderman (1975), and does not appear to be in accord with any specific agency guidelines. Generally, there seems to be no consensus for use of a particular conversion factor among the agencies. The Carcinogen Assessment Group advocated the use of mg/surface area/day. FDA, in 1979, rejected the use of conversion factors based on surface area ratios and advocated mg/ weight of total diet. The IRLG document stated "several species-conversion factors should be considered."

(4) Use of information comparing differences in metabolic processes and rates in experimental animals and humans: Most agency guidelines written in the past have advocated the use of metabolic and pharmacokinetic data to demonstrate interspecies differences, when such data is available. Typically, however, data pertaining to these areas is inadequate or lacking. In the view of CPSC, there was insufficient evidence available to consider interspecies differences in the present risk assessment. The lack of sufficient data and the need for more information was acknowledged in the Formaldehyde Panel report recommendation for future research: "the pharmacokinetics of formaldehyde and its interaction with target tissue should be studied in several animal species."

(5) Treatment of data when data from more than one species or strain is available: Most agency guidelines written in the past have not explicitly addressed this question. The IRLG document, however, does make an explicit statement: "If data on animals are used as the basis for estimating human risk, data obtained from the most sensitive animal species or strain tested are commonly recommended as the starting point for extrapolation. Of the available data, these are clearly the least likely to underestimate human risk. Use of data from less sensitive species or strains is justifiable only if there are strong reasons to believe that the most sensitive animal model is completely irrelevant to any segment of the exposed human population."

9. Describe any internal, internal-advisory (e.g., EPA's SAB), and external (e.g., NAS) scientific review of the initial analysis. What, if any, criticism was incurred?

CPSC has no formal internal review group. Within the Directorate of Health Sciences, there is an informal risk assessment work group consisting of staff persons knowledgeable in risk analysis. This group reviewed the document. In addition, all staff involved with or interested in formaldehyde reviewed the risk assessment.

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In addition, the analysis underwent an external review. Other IRLG agencies were asked to comment (EPA, FDA, and OSHA). EPA's review was particularly intensive. Ten people in three different groups were involved in the review process.

Outside experts who were involved in the review process were: Dr. Kenny Crump, a private consultant, Dr. David Gaylor of NCTR, an MIT group headed by Dr. Nick Ashford, and Dr. Charles Brown of NCI.

One criticism dealt with a refinement of the application of the linearized multistage model. In the initial risk assessment, the value of the upper 95% confidence limit of the lowest observed dose (2.1 ppm) was calculated, and a linear extrapolation from that value was arbitrarily assumed. Dr. Crump suggested that a more accurate assessment would be obtained if the upper 95% confidence limit of risk is followed to exposure levels below 2.1 ppm. In this refinement, linearity appears only at doses below 1 ppm.

Other criticisms centered around the choice of interspecies conversion factors. The assumption that the risk to rats at a particular concentration was equal to the risk to humans at the same concentration was challenged. Also, the calculation of duration of risk based on proportion of lifetime for a given species was questioned. No suggestions, however, were made on how to better incorporate such factors.

10. How were issues raised in the review(s) accommodated?

Following the suggestion of Dr. Crump (see Question C.9), the revised risk assessment refined the linearized multistage calculation used in the initial assessment. Instead of arbitrarily assuming linearity from the upper 95% confidence limit value of the lowest observed dose (2.1 ppm), the new analysis calculated values below 2.1 ppm. This recalculation defined a more precise linear function which led to a 2.4-fold reduction in the estimated risk.

11. What other issues arose concerning scientific data and their use? Describe dissenting opinion.

Interested parties were able to comment on the risk assessment after CPSC published an announcement in the Federal Register. The Formaldehyde Institute, CIIT, and others raised many objections. A major criticism focused on the choice of a linearized dose response curve at low levels of exposure. Critics questioned the bases for assuming a linear model and charged that it was excessively conservative and that there were reasons to believe that it was not scientifically plausible.

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On December 15, 1981 Dr. James Gibson, vice president and director of research for CIIT, presented to the CPSC staff an argument which would suggest a much reduced risk at low exposures from that predicted by CPSC's linearized model. Dr. Gibson reported that a physical mechanism for clearing formaldehyde from the nasal epithelium could substantially reduce the dose delivered to target cells. He reported that the respiratory epithelium is protected from foreign chemicals in inspired air by a layer of mucus, which can carry chemicals away from the nasal cavity by the propelling action of beating cilia. He stated that at high concentrations formaldehyde could saturate the mucus blanket and subsequently contact directly with target cells, but at low concentrations formaldehyde may be completely assimilated within the mucus blanket and removed without reaching the target cells. In essence, Dr. Gibson presented an argument for a threshold dose-response model.

CPSC's had stated in its public record that effects due to formaldehyde on the nasal epithelia are observed at low doses. CPSC cites the occurrence of benign tumors at 2 ppm in the CIIT rat study, and the occurrence of nasal irritation effects at concentrations as low as 0.25 ppm. Some might argue that these data suggest clearance may not be complete at these doses. In addition in a February 15, 1982 letter to Nancy Steorts, chairman, Consumer Product Safety Commission, Dr. Gibson cited studies conducted at CIIT which in his judgment demonstrated the importance of concentration rather than cumulative exposure to formaldehyde. He stated, for example, that “short exposures to 12 ppm caused severe disease, including ulceration and erosion of the lining of the nose after as little as 3 days of exposure. In contrast, there was no ulceration or erosion of the lining of the nose in the rats exposed to 3 ppm. Thus to estimate tumor incidence based on cumulative exposure without considering the more important issue of high concentration effects is scientifically invalid. Formaldehyde concentrations that are sufficiently high cause acute cell injury, cell death and ulceration of the nasal mucosa and may be associated with the induction of nasal tumors. However, in the absence of acute effects nasal tumors are not expected and do not occur....”

In CPSC's view severe ulceration is not a necessary condition for the induction of tumors. Rather, CPSC believes that the major effect of ulceration is to cause respiratory epithelial cells to be rapidly replaced by squamous cells, which appear to be more resistant to cytotoxic effects. It is the squamous cells, where the induction of tumors has been observed. This sequence of events does not imply, however, that tumors would not have occurred without ulceration.

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Another much debated issue was the question of the genotoxicity of formaldehyde. It is generally believed that carcinogens which are genotoxic exhibit a greater potency at low doses than carcinogens which are not genotoxic. There are scientific arguments which support the belief that genotoxic agents exhibit a linear nonthreshold response at the target site at low doses while nongenotoxic agents exhibit a threshold response. CPSC considers formaldehyde to be a genotoxic agent. Dr. Gibson believes that the genotoxicity of formaldehyde may not be expressed at low exposure:

> It also should be stressed that the results of various genetic toxicity studies are mixed; some are positive and some are not. Research by CIIT indicates that the potential genetic toxicity of formaldehyde occurs only in dividing cells. The increase in cell proliferation brought about by acute tissue damage due to high concentrations of formaldehyde produce such a circumstance. In the nasal mucosa, CIIT has shown that the normal rate of cell division is very low, and that the rate is not increased by formaldehyde concentrations of 0.5 or 2 ppm in rats or by 0.5, 2 or 6 ppm in mice. (Gibson letter to N. Steorts, Feb. 15, 1982.)

CPSC's position stated that although the results of mutational expression may be mixed, all the data are consistent with formaldehyde being a weak mutagen; negative results can be explained by the inability of formaldehyde to reach the target being assayed. Also, CPSC believes that although cell proliferation may be an important factor in cancer development, there are no data which show that it is necessary for formaldehyde to cause this effect in order for cancer to occur. CPSC believes that formaldehyde does not have to cause all stages of cancer development; background processes could interact with formaldehyde in causing cancer.

Another major criticism dealt with exposure assessment. Critics contended that the quality of the CPSC exposure data base was poor. They stated that the data was accumulated from many sources with “no common denominator and little or no controls,” and the prescribed analytical method lacked sensitivity at the measured exposure levels.

CPSC maintained that its method of analysis and the assumptions used caused consistent underestimation of exposure.

Finally, critics contended that the external peer review of CPSC's risk assessment involved scientists with a policy orientation similar to CPSC's (i.e., an orientation partial to the use of linear extrapolation through zero models). Thus, they believe that the peer review did little to challenge major issues of the analysis.

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12. Is the substance subject to past or possible future regulatory actions in other programs? If so, did the program office coordinate with other agencies or programs? (See Question B.10).

D. INTERPRETATION

1. What role did risk assessment have in the final agency document where standards were established to control the chemical?

The carcinogenic risk assessment played a vital role in setting the final standard, which was to ban the use of UFFI in residences and schools. Previous to the development of this risk assessment, CPSC had considered regulation solely on the basis of irritation effects and hypersensitivity (45 FR 39434, June 10, 1980). The proposed action was not a ban, but a rule that would require manufacturers of UFFI to give hazard information to prospective purchasers. The basis for the difference between these two regulations depended heavily on CPSC's determination that as high as 50 out of a million increased deaths per lifetime could occur from the use of UFFI.

2. Were there variations--over time or across agency programs-in the assumptions used? Were these variations significant to the final risk assessment?

Variations Over Time

In the spring of 1981, EPA staff, from the Office of Toxic Substances (OTS), recommended that priority attention be given to formaldehyde and drafted a notice to appear in the Federal Register (FR) saying that formaldehyde would be considered for regulatory action under Section 4(f) of the Toxic Substances Control Act (TSCA). The EPA draft notice stated, “EPA has determined that there may be reasonable basis to conclude that some exposures to formaldehyde present a significant risk of widespread harm to humans. Therefore, the agency is initiating action to investigate those exposures of greatest concern and determine whether they lead to unreasonable risks.” Shortly after this determination, Anne Gorsuch, the newly appointed EPA Administrator, took office. She did not sign the notice and it did not appear in the Federal Register. On February 10, 1982, Dr. John Todhunter, the new Assistant Administrator for Pesticides and Toxic Substances sent a formal memorandum to Ms. Gorsuch recommending that formaldehyde should not be considered as a priority chemical for regulation. In his judgment, the earlier OTS risk assessment was deficient. One major point was his characterization of the exposure estimates as poor in quality. He also found

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fault with the inference options used for hazard identification and dose-response assessment. Specifically, he stated, "The PRL-1 (the name given to the 1981 OTS risk assessment document, which formed the basis for the draft notice) concludes that formaldehyde is an animal carcinogen. It down plays a number of negative bioassays which suggest that its effects may depend highly on species, route and site. No attempt was made, also, to address the question of mechanism of action or other physiological/ biochemical questions relevant to the extrapolation from rat to human even though such information was available from CIIT." He was also critical of the PRL-1 treatment of the dose-response data from the CIIT rat study. "The risk calculation used by OTS included the 5.6 ppm exposure level as a non-zero incidence data point. CIIT has since determined this point to be statistically no different than the 0 ppm and 2.1 ppm exposure results.* If this 5.6 ppm exposure were treated as a zero response point, the risk estimates...would shift...to yet lower values." Furthermore, Dr. Todhunter stated that even if one were to accept the calculated levels of risk determined in PRL-1, they would not be sufficiently high to trigger action under Section 4(f):

> As can be seen, nearly all individual risks fall into the range $1 \times 10^{-6} - 1 \times 10^{-4}$. This places them into a range in which priority action is often not considered...if the human risk were real, the magnitude of individual risks do not seem to compel a "fast track" approach.

Somewhat parallel developments occurred at the Occupational Health and Safety Administration (OSHA). OSHA officials had been planning to release a joint statement on formaldehyde with the National Institute of Occupational Safety and Health, but in July 1981 this decision was reversed. A petition brought by the United Auto Workers requesting an emergency standard for formaldehyde was denied by OSHA on October 26, 1981.

* CIIT determined that the incidence of 2 malignant tumors versus zero in the study controls was not significant. Others might argue that the incidence is significant if historical control data is considered.

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Variations Across Agencies

Thus far, CPSC is the only agency to issue a final rule on formaldehyde use. It based this decision on a risk assessment similar in many aspects to the EPA PRL-1 document which was criticized by Dr. Todhunter in his February 10, 1982 memo to Ms. Gorsuch. Even though the Todhunter memo does not specifically address the CPSC risk assessment, the issues raised therein do serve to highlight differences of interpretation of risk assessment data between CPSC and EPA. It should be noted that the degree to which the two agencies differ increased significantly with the advent of the new administration at EPA in the spring of 1981 (see Question B.10).

In specific terms, Dr. Todhunter states that, “Formaldehyde appears, therefore, to exhibit considerable species specificity with the rat, the most sensitive species so far tested. Concern that formaldehyde gas may induce tumors in humans should be tempered by this observation that formaldehyde carcinogenicity appears to have a high degree of species specificity and a strong dependence on route of exposure.” CPSC's position is that the strong evidence of carcinogenicity in rats provides strong evidence of carcinogenicity in humans, especially in light of the limitations of the negative studies.

Dr. Todhunter also argues that at low levels of exposure (1-2 ppm) formaldehyde may exhibit a toxicity much reduced from that predicted by the linearized model utilized by CPSC. He sites findings by CIIT to support this argument. These are:

(1) Reversibility of hyperplastic and metaplastic effects of formaldehyde at low exposure levels or short exposure times;
(2) The presence of endogenous levels of formaldehyde in tissue ranging from 3-12 ppm;
(3) The absence of cytotoxic effects from formaldehyde levels at or below 1.0 ppm in air;
(4) Evidence to suggest that formaldehyde acts as a promoter.

CPSC rejects the contention that these arguments suggest a nonlinear dose-response relationship at low dose, with greatly reduced risk at low levels of exposure. CPSC believes that formaldehyde is both an initiator and a promoter and that the reversibility and promotional aspect (points 1 and 4) do not argue against linearity at low dose, especially when the property of initiation is considered. CPSC further believes that the absence of cytotoxic effects at 1.0 ppm has not been at all demonstrated;

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and that, nevertheless, the concept of cytotoxicity is not relevant to the shape of the dose-response curve at low dose where initiation and promotion aspects of formaldehyde are still likely to be operating. Finally, CPSC believes the endogenous levels of 3-12 ppm are also not derived from any existing data, and not relevant to the argument. CPSC notes that virtually all formaldehyde in tissues is not free, but bound in a different chemical form with entirely different chemical and biological properties.

Another point of departure is interpretation of data on benign tumors. Dr. Todhunter does not directly address the question of benign tumor incidence in the formaldehyde rat study. He does address the topic generically when suggesting a definition for the term "serious." (Part of the criteria for initiating Section 4(f) is the determination of "serious or widespread harm.")

> The concept of "serious" harm would have more utility in the consideration of gene mutational events or birth defects than in the case of cancer since malignant neoplasms in general are serious. Section 4(f) also draws a distinction between benign and malignant growths by use of the term "cancer" rather than "tumors."

The CPSC risk assessment did not consider benign tumors, mainly because the information regarding their incidence was not reported to CPSC by CIIT at the time. CPSC's risk assessment does state, however, that inclusion of benign tumor data would lead to an increased prediction of risk.

Another point of difference regarding the interpretation of available epidemiological data for formaldehyde. Dr. Todhunter states, "There is a limited but suggestive epidemiological base which supports the notion that any human problem with formaldehyde carcinogenicity may be of low incidence or undetectable. It would not appear reasonable to say that a significant risk situation exists from this data." CPSC, after reviewing epidemiological evidence from written statements and oral presentations at public meetings concluded that none of the epidemiological studies to date were of sufficient statistical sensitivity or quality to draw any valid inferences regarding the magnitude of carcinogenic risk to humans. Scientists at NIOSH and a working group of IARC concurred with the CPSC evaluation.

The two agencies differ sharply on the levels of risk that should trigger concern. Dr. Todhunter states, "In terms of individual lifetime cancer risks, the various federal agencies do not tend to regulate risks of 1×10^{-5} or lower and tend to be ambivalent about risks between $1 \times 10^{-4} - 1 \times 10^{-5}$." He states further that, "In OPTS, the relative risk range of 1×10^{-4} to 1×10^{-6} or lower has been a low concern range in general." CPSC's estimated risk for inhabitants of UFFI residences is $0.6 \times 10^{-4} - 0.9 \times 10^{-4}$. Also, in a proposed rule regarding chemical compounds in food-producing animals, FDA

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suggested a risk of 1 x 10^{-6} over a lifetime as a trigger for regulatory action: "An increase in the level of risk to 1 in 10,000 might significantly increase human risk. It is difficult to choose between 1 in 1 million and 1 in 10,000 but the agency chose the more conservative number in the general interest of protecting human health," (FDA, 1979).

Finally, Dr. Todhunter states, "The results of the CIIT bioassay are, however, sufficient to establish that formaldehyde is a potential animal carcinogen with mode and degree of exposure quite important to the outcome." CPSC's opinion is that formaldehyde is a definite animal carcinogen and should be a presumed human carcinogen.

3. To the extent there were issues/concerns about questions of science, would the outcome have been improved by:

- A better system of in-house scientific review?
- Review by an outside scientific organization?
- Coherent federal guidelines on carcinogenic risk assessment?
- Better agency guidelines on the performance of risk assessment?
- Improved agency decision procedures?

In the view of the author of this case study, many of the issues and concerns about the risk assessment of formaldehyde revolved around a complicated mix of risk assessment policy judgments and scientific judgments. On both sides of the debate, there was often no clear distinction drawn between scientific and policy judgments. At the time the risk assessment was prepared, there were no uniform federal guidelines for carcinogenic risk assessment in use. Such guidelines may have been helpful in providing a scientific and policy framework to support the CPSC risk assessment, and in drawing sharper distinctions between scientific and policy judgments employed in risk assessments. Critics' comments may have focused on the generic scientific and policy issues raised in the guidelines. Furthermore, adherence to guidelines may have fostered a greater degree of explicitness in the use of inference options applied, and reduced the degree of inconsistency in interpretations among the agencies (i.e., CPSC and EPA).

The CPSC risk assessment may have benefitted from peer review by an independent science advisory panel. In general, this is good practice for all federal risk assessments.

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E. PERFORMANCE CONSIDERATIONS

1. Ability to obtain scientific information.

CPSC staff felt that there was a problem obtaining pertinent data from CIIT as it was needed. Time-to-tumor data and information on benign tumors was withheld until the release of the full final CIIT report in February 1982 (three months after the completion of the final CPSC formaldehyde risk assessment). Consequently, time-to-tumor and benign tumor data were not considered in the final risk assessment in any quantitative fashion. Both pieces of information would have increased the risk had they been factored into the risk assessment.

Other data, which could have weighted the evidence toward a reduced risk, was also withheld by CIIT, although the results of these studies were presented in part in November 1980 at a CIIT conference. One study dealt with evidence suggesting that formaldehyde was not genotoxic. Another report was an epidemiology study which yielded negative results. In the view of CPSC, detailed documentation of these results have, as yet, not been released.

One of the most important pieces of scientific information is the pathology slides from the initial CIIT study. Six pathologists representing IRLG were permitted to review the slides in the middle of the study (January 1980). No further review has been permitted since then, although CPSC and the IRLG Formaldehyde Task Group had requested such a review.

CIIT maintains the position that, as a matter of policy, they do not release data to any one party alone (i.e., the government); that the release of data has to be made public, and is not privy to any one interest group.

2. Credibility of assessments, likelihood that interested parties would accept them as definitive.

Hazard Identification

The Formaldehyde Panel, IARC, NIOSH, the Selikoff and Hammond Committee Report to the American Cancer Society, the heads of NCI, NIEHS, and NCTR and three distinguished scientists at New York University Medical Center have all concurred that formaldehyde is a definite animal carcinogen and should be considered to pose a human carcinogenic risk. Some interested parties could dispute these assertions, but it is likely that most would not.

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Quantification and Characterization of Risk to Humans

Representatives of CIIT and the formaldehyde industry were highly critical of CPSC's quantitative risk assessment. As detailed in Question C.11, two main points of criticism focus on the choice of the dose-response curve, and the quality of CPSC's exposure data.

3. What was the extent of diversity of policy orientations represented within the assessment group itself. What was the degree to which interest pressures would be exerted from outside the assessment group? What was the responsiveness of the assessment to these diverse interests?

Both the hazard identification and the quantification of risk to humans were performed solely by federal scientists. Hence, the extent of diversity of policy orientations was quite limited. It does not appear that there was any degree of interest pressure exerted from outside the group.

4. What were the time and resources necessary to complete the risk assessment?

Hazard Identification Assessment

The federal panel consisted of 16 scientists working part-time (actual percentage unknown) for 9 months.

Characterization of Risk to Humans

Seven CPSC staff persons worked full or part-time over two years collecting and reviewing data and reviewing comments.

The cancer risk assessment document (excluding the effort needed to obtain exposure data) required one person working full time for one year.

5. Responsiveness of assessment agenda to public concerns, interest group concerns, professional concerns, and emergence of new scientific data.

It appears that CPSC responded to public concerns regarding irritation and sensitivity effects with cautious but deliberate action, and it responded to the newly emerging information on formaldehyde as a potential human carcinogen with swift, decisive action.

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As described in detail in Question A.2, the first public concerns voiced in October 1976 regarded irritation effects from formaldehyde release in UFFI residences. Over the next couple of years, several thousand similar complaints were filed with CPSC. In order to obtain more detailed information on the full extent of human health concerns, CPSC asked the National Academy of Sciences, in May 1979, to prepare a comprehensive report. The report was completed in March 1980. Public hearings were held from December 1979 through February 1980 as industry, state and local government officials, scientists, and others testified on the question of UFFI and formaldehyde release. As a result of all this activity, on June 10, 1980, CPSC issued a proposed rule which would require UFFI manufacturers to label their products giving specified performance and technical information to prospective purchasers. This rule was never made effective because in the view of CPSC the new emerging cancer data required more stringent rulemaking.

The first preliminary data from the CIIT rat studies was presented to CPSC in October 1979. One month later, a briefing package prepared by staff was sent to the commissioners. In January 1980, an IRLG task force visited CIIT to verify the findings. In April 1980, the CPSC-requested Formaldehyde Panel was formed to assess all current literature and make recommendations as to the severity of health effects. The final report in November 1980 concluded that formaldehyde was a potential human carcinogen. In February 1981, CPSC published a proposed rule to ban UFFI. In October 1981, the final CPSC cancer risk assessment was completed. In April 1982, CPSC published a final rule to ban UFFI.

6. Ability of the risk assessment to identify research needs.

Interest in the possible harmful effects of formaldehyde generated an abundant listing of research needs. The CPSC-sponsored National Academy of Sciences study on health effects of formaldehyde (March 1980) identified twelve research needs including the areas of carcinogenicity, reproduction and teratogenic effects, sensitivity of population subgroups, pharmacokinetic studies, sources and fates of formaldehyde, and percutaneous penetration.

The Formaldehyde Panel report identified research needs in teratology, animal reproduction, human reproduction, mutagenicity, carcinogenicity (pharmacokinetics, other routes of administration, neoplastic transformation of mammalian cells), epidemiologic research, and the ability of formaldehyde to interact with other pollutants.

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A major research effort has already begun with the goal of obtaining more definitive results from epidemiological data. Both NCI and NIOSH are examining data on large numbers of workers with a history of high formaldehyde exposure. Many of the other needs have been or are being assessed by research programs both within and outside the government.

7. Extent to which risk assessment impeded or facilitated regulation.

Informed high level CPSC staff believe that the risk assessment did both. It facilitated regulation by giving the assessors an idea of the range of risk. It impeded regulation because the calculated numbers create a false impression of certainty that leaves the assessment vulnerable to attack by critics opposed to regulation. Staff felt there was an urgent need to define the limits of risk assessment more clearly and accurately.

8. Were related risk assessments consistent?

This question has been covered in Questions B.10 and D.2.

9. Extent to which there is an explicit distinction between weights accorded to scientific factors and policy factors.

As mentioned in Question C.5, major areas of uncertainty affecting the results of quantitative risk assessment are choice of the low dose extrapolation model and choice of the interspecies conversion factor. Choices can be made by adhering to two criteria: (1) how well does the model fit the data, and (2) how biologically plausible is the model. Apart from these science-oriented criteria, choices can also be made solely for policy reasons. For example, an agency may wish, in the face of uncertainty, to err on the side of caution. Therefore, it may adopt a policy of choosing a conservative model.

The CPSC risk assessment calculates two dose-response curves: the linearized multistage curve, and the “best-fit-of-data” curve. It strongly endorses the linearized multistage curve, which is the more conservative model. However, CPSC's stated reason for endorsing this model was purely scientific. It considered it to be more biologically plausible than the “bestfit-of-data” model. If a policy factor did go into the decisionmaking process, it was not explicitly stated in the risk assessment document.

CPSC's choice of an interspecies conversion factor was based on a paper by Mantel and Schneiderman (1975), although no concrete scientific reasons were given for the choice. It is not clear how conservative this factor is relative to other conversion factors.

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10. Mode and frequency of communication between assessors and regulators.

Hazard Identification

The Formaldehyde Panel, in its appraisal of formaldehyde as a potential human carcinogen, appeared to be acting entirely independently of agency regulators.

Characterization of Risk

CPSC appears to have organizational separation between the assessors and the regulators. The assessors, consisting of staff from the Directorate of Health Sciences, performed their function without apparent contact with or guidance by the program team and the commissioners, who are the regulators.

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NITRITE

Catherine St. Hilaire

A. BACKGROUND AND CONTEXT

1. Describe the chemical and its uses.

Nitrogen exists in nature in various forms one of which is nitrate. Nitrites are chemicals that form when living systems act upon nitrate salts, which are widely distributed in soil, plants, and water, or upon nitrogen in other forms.

Nitrite inhibits the growth of various microorganisms found in foods, including Clostridium botulinum. It also helps to maintain the typical reddish color of cured meats, inhibits the development of rancidity in meat and fish, and may contribute to the flavor of cured products. The addition of nitrite to meats has been permitted in the U.S. since 1925. It is currently added to meats and fish primarily as an antimicrobial. Approximately 25% of all meats consumed by the U.S. population contain added nitrite.

2. Describe how the question of risk was elevated to the agency level.

There are two aspects related to the risks of nitrite ingestion:

(a) The contribution of nitrite to the formation of nitrosamines (a large group of chemicals over 90 percent of which are carcinogens in animals).

NOTE: This case study describes assessment procedures and summarizes issues and interpretations raised by others, but it is not intended to present independent positions or interpretations on either scientific or policy matters. The case has been reviewed by individuals outside the study project who are directly familiar with the federal analyses and decisions described; however, responsibility for the paper rests with the author, and it does not necessarily reflect the judgment of the Committee on the Institutional Means for Assessment of Risks to Public Health or the National Research Council. It has not been subjected to internal review procedures that apply to reports prepared by NRC committees.

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(b) The carcinogenicity of nitrite per se.

Two agencies are involved in the regulation of the use of nitrite in cured meats--USDA and FDA. Interest in risks associated with nitrosamine formation stem from findings in the 1970s that nitrosamines were found in a number of foods. Earlier findings had also indicated that nitrosamines could form in the body following ingestion of nitrite. In 1970, the USDA and FDA formed a group to coordinate research activities in this area.

In 1972, the USDA was petitioned to ban or greatly reduce the use of nitrite. The petition was denied. Based on additional evidence of the presence of nitrosamines in bacon, the Secretary of Agriculture appointed an advisory Expert Panel on Nitrites and Nitrosamines. In September 1974, the Panel provided a preliminary report which prompted USDA to propose several regulations that reduced the levels of nitrite permitted in various meat products.

In 1978, the Panel issued its final report recommending levels of nitrite in a variety of products. USDA published a final regulation on the use of nitrite in bacon. Further action on the rules proposed by USDA in 1975 and the other recommendations of the Expert Panel were halted in mid-1978 by a report that nitrite per se was carcinogenic in animals.

3. Under what statutes and agency jurisdiction does the chemical fall? What statutory tests governed the decision?

The Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.) (FD&C Act), as amended on September 6, 1958, by the Food Additives Amendment (21 U.S.C. 348), requires FDA to establish regulations prescribing the conditions under which a food additive may be safely used. The act defines a “food additive” as any substance which becomes or may be expected to become a component of food, either directly or indirectly, or which may otherwise affect the characteristics of the food. Before a regulation can be established, the additive must be shown to be safe and functional for its intended uses (i.e., it must accomplish the effect for which it is to be used--preservatives must preserve).

The act states, however, that no food additive shall be deemed safe if it is found to be carcinogenic (induce cancer) when ingested by man or animal or if it is found, after tests which evaluate the safety of food additives, to induce cancer in man or animal. This provision is commonly known as the Delaney Clause. Under this provision if a substance is shown, based on scientific analysis, to induce cancer when fed to test animals, FDA cannot allow its use.

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In addition, if after its approval, a substance is found, by adequate scientific evidence, to be carcinogenic, its use must be banned. If the evidence is not sufficient to prove that the substance is carcinogenic but does raise substantial unresolved questions about its safety, the general safety clause of the act (21 U.S.C. 348(c)(3)(A)) would require the banning of the substance.

The requirements for revoking approval of a food additive are not as demanding under the general safety clause as under the Delaney Clause. Instead of proof that a substance causes cancer, FDA is required only to present new evidence raising a substantial unresolved question about the safety of an approved substance. FDA does not have the burden of proving that a substance causes cancer or that it is otherwise unsafe; FDA has only to present new evidence that raises a substantial safety question. The burden then is on the manufacturer to resolve the question by showing that the substance is safe.

The Food Additives Amendment exempts certain categories of food ingredients from the definition of "food additive." One such category includes those substances that have "prior sanctions." A substance has a prior sanction if its use in food was sanctioned or approved by FDA or USDA before September 6, 1958, the effective date of the amendment. Such approvals were granted under provisions of the FD&C Act, the Poultry Products Inspection Act (21 U.S.C. 451 et seq.), and the Federal Meat Inspection Act (21 U.S.C. 601 et seq.).

Because prior sanctioned substances are not covered by the definition of "food additive," the provisions of the Food Additives Amendment, including the Delaney Clause, do not apply to them. The three laws under which prior sanctions were granted provide, however, that the public is to be protected from adulterated food products. They state that food is adulterated if "it bears or contains any poisonous or deleterious substance which may render it injurious to health." Thus, if competent scientific evidence demonstrates a reasonable possibility that some consumers may be harmed by eating food containing a prior-sanctioned substance, the food is adulterated and cannot be introduced into the food supply.

USDA is responsible for assuring that the Nation's meat and poultry supply is safe, wholesome, and properly labeled. While FDA has primary responsibility for approving the use of substances identified as food additives, USDA has the additional responsibility to determine that an FDA-approved additive may be used in meat and poultry products. This responsibility includes determining that the approved additive will serve a useful purpose and establishing a minimum amount of the additive necessary to achieve that purpose. USDA also restricts and monitors the use of approved additives to assure that requirements for safe use are met.

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4. What was the decision schedule?

May 2, 1978	Top FDA and USDA officials are briefed on the study showing that nitrite is carcinogenic. (No written report submitted.)
May 16, 1978	Special Ad Hoc Working Group begins review of study and development of regulatory options.
July, 1978	USDA and FDA seek Attorney General's ruling on their plan to phase out nitrite and arrange for joint news conference announcing their decision concerning nitrite. FDA's “50-page paper” outlining agency's decision to phase out nitrite is leaked. FDA-USDA news conference is cancelled.
August 28, 1978	Interagency Working Group (IAWG) on nitrite meets.
October 18, 1978	2 pathologists on the IAWG reported that pathological assessment of tumors in MIT study may be faulty.
March 30, 1979	FDA contracted the UAREP, a nonprofit consortium representing pathology departments of 15 universities to review pathological slides of MIT study.
March 30, 1979	The Attorney General found that there was no legal basis for a phaseout and, if nitrite causes cancer, the agencies were to assure its orderly removal from commerce.

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March 30, 1979	Sec. of HEW and USDA hold press conference to announce intention to propose legislation to prohibit FDA and USDA from banning before May 1, 1980 and to give FDA and USDA the authority to phase out nitrite, if it is determined to be carcinogenic, over a period of years, dependent upon the development of alternative means of food preservation.
Spring 1979	A number of bills are introduced in Congress to prevent the agencies from banning or phasing out nitrite.
August 15, 1980	UAREP report fails to confirm carcinogenicity of nitrite--IAWG issues final report stating nitrite is not a carcinogen.
August 1980	FDA and USDA announce that no action will be taken against nitrite.
September 1980	USDA - FDA undertake joint contract with the NAS for review of health effects of nitrate, nitrite, and N-nitroso compounds.
December 1981	NAS releases final report confirming that nitrite per se is not a carcinogen but that it may contribute to formation of carcinogenic nitrosamines.

B. CHARACTERIZATION OF RISK TO HUMANS (Sections B & C were combined)

1. What health endpoints were evaluated?

Carcinogenicity (as detected in animal tests).

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2. What were the key data available for review?

A study conducted for the FDA by Dr. Paul Newberne, a senior pathologist at MIT, which showed that nitrite caused a statistically significant increase in the number of lymphoid tumors in rats.

In this large lifetime study conducted for the Food and Drug Administration (FDA), sodium nitrite was administered to groups of approximately 68 male and 68 female Sprague-Dawley rats under a variety of conditions. Groups 1 to 5 received 0, 250, 500, 1,000 or 2,000 mg/kg sodium nitrite in the diet, and groups 6 and 7 received 1,000 or 2,000 mg/liter in drinking water. For these groups, an agar-based semisynthetic diet was used. For groups 9 to 11, a commercial chow diet was substituted, and sodium nitrite concentrations of 0, 1,000 or 2,000 mg/kg diet were fed to the animals. Groups 13 and 14 were given a refined casein diet containing nitrite at 0 or 1,000 mg/kg, while another two groups, 15 and 16, were fed the original semisynthetic diet containing nitrite at 0 or 1,000 mg/kg. Each of the latter two groups contained only 34 animals--the dams that supplied the pups for groups 1 and 4. Groups 17 and 18 were also fed the semisynthetic diet containing nitrite at 0 or 1,000 mg/kg. Groups 1 through 16 were exposed prenatally, while groups 17 and 18 were exposed at 21 days. Groups 8 and 12 served as positive controls and received urethane (2,000 mg/liter) in drinking water or in the semi-synthetic diet, respectively. The rats survived the sodium nitrite regimens well, the only adverse effects being a loss of weight in groups receiving 2,000 mg/kg in their diet and, to a lesser extent, in groups receiving 2,000 mg/liter in drinking water.

Histopathologic assessment of the tissues indicated that by considering all the groups receiving sodium nitrite together, there was a statistically significant excess of lymphoid tumors ($p<0.01$, based on chi-square analysis). This was reflected especially in the groups receiving sodium nitrite in drinking water, where the excess of lymphoid tumors was statistically significant, but the results were not significant in the other groups treated with sodium nitrite.

In addition to malignant tumors of the lymphatic system, an alteration referred to as immunoblastic cell proliferation was observed in the spleen and, occasionally, in the lymph nodes of some members of all groups except the positive controls (groups of 8 and 12). The incidence of this abnormality in nitrite-treated animals, however, was greater (11.2%) than in the untreated animals (7%). The disease in humans, which is histologically similar to that observed in rats, is considered by some to develop into lymphoma; others consider it not to be preneoplastic.

These results were taken as an indication that nitrite is an enhancer or promoter of carcinogenesis in rats.

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3. Who performed the initial analysis?

The FDA commissioner appointed a special intra-agency Ad Hoc Working Group to review the data and to make recommendations. The Chief Counsel was responsible for overall development of the regulatory policy and the Acting Director, Bureau of Foods was responsible for directing the scientific review of the study. The other members of the Ad Hoc Working Group were the Commissioner, Deputy Commissioner, Executive Assistant to the Commissioner, Associate Director of Regulatory Affairs, Director of Health Affairs, and two staff scientists from the Bureau of Foods.

4. To what extent were the results presented quantitatively? What factors influenced the degree of quantification?

The data from the MIT study were used to estimate leukemia-like cancer risks to humans (Table I).

5. How was uncertainty described in reaching the final interpretations? Were crucial assumptions made explicit?

Assumptions that had to be made were listed:

(a) That humans consume 1/4 of the amount of nitrite initially added to cured products.
(b) That humans and rats are equally sensitive to the cancercausing effect of nitrite.
(c) That there is a linear relationship between the incidence of cancer resulting from the doses ingested by the rats and that resulting from the doses to which the average American is exposed.
(d) That the risk of cancer from nitrite is evenly spread over the American population.

6. How were qualitative factors dealt with?

A discussion of the validity of animal tests was included in a document (the “50-page paper”) describing the basis for FDA's and USDA's action regarding nitrite. This discussion did not emphasize the uncertainty of extrapolating from animals to man but instead served to refute arguments that have been made against this use of animal tests.

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TABLE I: ESTIMATED LIFETIME CANCER RISK FROM NITRITE* (From the "50-page paper")

Based on Incidence in Test Rats of:		
Dietary Source of Nitrite	Lymphomas	Lymphomas + Immunoblastic Cell proliferation
All sources	1/3450-1/2040 (2.9 - 4.9)	1/1560-1/794 (6.4 - 12.6)
Cured meats (200 ppm nitrite)		
1.6 oz/day	1/16,700-1/9090 (0.6 - 1.1)	1/7140-1/3700 (1.4 - 2.7)
8 oz/day	1/3230-1/1890	(6.8 - 13.5)
(40 ppm nitrite)		
1.6 oz/day	1/100,000-1/50,000 (0.1 - 0.2)	1/33,300-1/20,000 (0.3 - 0.5)
8 oz/day	1/16,700-1/943 (0.6 - 10.6)	1/7140-1/3700 (1.4 - 2.7)

* The two risk estimates in each case are based on: (1) the amount of nitrite added to the rats' food or water; and (2) the average amount of nitrite to which the rats were actually exposed at each dose level. The numbers in parentheses are the estimated lifetime cancer risks per 10,000 population.

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Other key qualitative factors were neglected, including the basis for concluding that the tissue changes in the rat spleen were actually related to leukemias. This problem awaited scientific critique and eventually led to the refutation of the FDA conclusion. Other factors were the absence of a dose-response and a charge that the different groups of test animals became mixed during the course of the experiment.

7. What qualitative factors affected the weighting of data? Were such criteria explicit and in accord with any general guidelines?

The only qualitative factors discussed in this analysis were:

(a) The acceptance of animal tests conducted at high doses (this is consistent with IRLG guidelines.)
(b) The assumption that low dose effects are linearly related to high dose effects, i.e., effects are directly proportional to dose even at lower doses. (This is consistent with IRLG guidelines.)

8. Describe any internal, internal advisory, and external scientific review of the initial analysis. What, if any, criticism was incurred?

Apparently, there was no internal or external peer review of the initial analysis prior to the Commissioner informing the Secretary of HEW of the plan to phase out nitrite.

In August 1978, an Interagency Working Group composed of scientists from FDA, USDA, and NIH was convened to review the scientific data of the MIT study. At the same time, the study results were sent to outside reviewers.

The following criticisms were made:

(a) The method of showing statistical significance (combining all treated animals in one group) was improper.
(b) The control groups had an unusually high incidence of lymphomas.
(c) Dose-response was not clearly demonstrated.
(d) Additional studies in another strain of rat and another species should be conducted before reaching a conclusion.

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(e) The possibility that the tumors were caused by nitrosamines could not be ruled out.
(f) The accuracy of the pathology diagnoses was questioned by IAWG pathologists who reviewed some of the tissue slides.

9. How were the issues raised in the review(s) accommodated?

The major issue was the question of pathological diagnoses. The Interagency Working Group on Nitrite Research reviewed a sample of histological slides and decided that there was sufficient difference of opinion in the diagnoses to warrant a further evaluation of the histopathological findings. The Universities Associated for Research and Education in Pathology (UAREP), a nonprofit consortium of 15 universities organized to carry out education and research activities in pathology, was selected by the FDA to review the slides. A Joint Committee of Experts, which was established by the UAREP to perform this review, diagnosed fewer lymphomas than had originally been reported. The disparity between the two series of diagnoses involved the differentiation of lymphomas from extramedullary hematopoiesis, plasmacytosis, or histiocytic sarcoma. Furthermore, the committee was unable to confirm the diagnosis of immunoblastic hyperplasia.

In its final report to the FDA, the Government Interagency Working Group summarized its assessment of the UAREP committee's findings as follows:

> The major result of the histopathology review was that most of the lymphoma diagnoses originally reported were not confirmed. A relatively high incidence of lymphomas had been reported by Dr. Newberne, [the scientist who conducted the original study] with a significantly increased incidence in the total combined treated groups as compared to combined controls. The UAREP pathologists, on the other hand, diagnosed very few lesions as lymphoma, with a resulting reduction of incidence to approximately 1% among treated and control groups. This rate of lymphoma incidence is similar to that usually seen spontaneously in Sprague-Dawley rats.
>
> UAREP pathologists did report a greater than 1% incidence of other types of tumors, including histiocytic sarcomas, angiosarcomas, liver neoplasms, ear duct tumors, pancreatic tumors, pituitary tumor, and mammary tumors. However, after statistical analysis and careful review by the IAWG, no demonstration could be found that the increased incidences of these tumors were induced by the ingestion of sodium nitrite.

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10. What other issues arose concerning scientific data and their use? Briefly describe dissenting opinion.

See question # 8

11. Is the substance subject to past or possible future regulatory actions in other programs? If so, did the program office coordinate with other agencies or programs?

The use of nitrite, especially in terms of the amounts permitted in various products, has been regulated in the past (and is subject to future regulation) by the USDA. In the case of the planned phaseout of nitrite, FDA informed USDA of its activities--the original announcement was to have been made jointly by the Secretaries of HEW and USDA.

C. INTERPRETATION

1. What role did risk assessment have in the final agency document where standards were established (proposed) to control the chemical?

(a) Risk assessment was used to show the reduction in risk associated with a decrease in the amount of nitrite added to bacon from 120 ppm to 40 ppm.
(b) Risk assessment was not used to compare risks from cancer with risks from botulism (if nitrite were eliminated). The Ad Hoc Working Group felt the data were insufficient to derive such an estimate.

It seems clear that the risk assessment was performed after the decision to regulate had been made. Historically, both the Commissioner of FDA and the Assistant Secretary of Agriculture at that time believed that nitrite should be reduced based on the nitrosamine potential. The latter individual had been frustrated by the seeming requirement that nitrite itself be carcinogenic not just a precursor to nitrosamines in order to remove it from the food supply. Thus, when the data apparently indicating a direct carcinogenic effect emerged, the premise upon which nitrite could be removed from food was obtained and led immediately to the development of regulatory strategies.

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2. Were there variations in the assumptions used? Were these variations significant?

Two risk assessments have been performed by FDA:

(a) in the original Working Group Document (described in preceding questions).
(b) in a subsequent report of the Nitrite Task Force (formed within the Bureau of Foods of FDA).

The second assessment differed from the first in the following ways.

(a) Newberne revised his own data after the original risk assessment was done, the second assessment uses the revised data.
(b) Equal sensitivity to nitrite between rats and humans was assumed on a mg/kg-body-weight basis rather than a concentration-in-the-solid-diet basis.
(c) In the earlier assessment, it was assumed that 1 ppm of nitrite in water = 1 ppm nitrite in solid diet. The second assessment assumes 1 ppm in water = 2 ppm in diet.
(d) Different estimates of daily nitrite intake for humans were used.

The second estimate was approximately 9% of the original estimate.

(The NAS also did a risk estimate for cancer risks from nitrite; however, their estimate of carcinogenic risk was based on the contribution of nitrite to the formation of nitrosamines--not as a direct result of exposure to nitrite.)

3. To the extent that there were issues/concerns about questions of science, would the outcome have been improved by coherent federal guidelines on carcinogenic risk assessment?

Yes. Despite the fact that the major flaw in the interpretation of the study stemmed from differences in pathologic diagnoses that cannot be addressed by inference guidelines, there were many other scientific issues that were not appropriately considered in the initial assessment of risks done by FDA. Adherence to comprehensive guidelines would have required that these issues by looked at more carefully and be addressed in the risk assessment document. Such consideration may have led to a more intense peer review of the study and its interpretation by FDA.

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In this case, peer review of agency decisions and the science underlying the decisions is probably more important than the use of risk assessment guidelines. Vigorous peer review did not enter into the process until the decision to regulate had already been made. Normal methods of FDA review were not followed for reasons that, at the time, appeared justifiable. In my opinion, it is likely that the normal peer review procedure would have revealed the fatal flaws in the MIT data since the normal procedure* would have called for the formation of an IAWG and it was in the Working Group that the questions about the study's pathology diagnoses were first raised. In addition, more stringent agency oversight of projects, such as the Newberne Study, which have major policy implications, might have averted the situation even earlier in the process.

D. PERFORMANCE CONSIDERATIONS

1. Ability to obtain relevant scientific information.

FDA contracted for this study. One way to approach this question is to focus on the importance of quality control and peer review/oversight of FDA-sponsored research. A GAO report was highly critical of FDA monitoring of the MIT study. Also, GAO recommended that research guidelines should be developed for design, data-recording and reporting, and statistical evaluation for carcinogenicity assays. Thus, FDA's ability to get reliable information in this case was dependent on its own foresight in planning the study and its commitment to ensuring that the experiment was conducted and interpreted properly. A major consideration leading to inadequate oversight was the high regard FDA scientists had for Dr. Newberne and his institution--MIT. As it turns out, a major portion of his pathological diagnoses was done by students not Dr. Newberne himself.

* USDA and FDA do not have a formal written policy for evaluating scientific information concerning the safety of food additives. There is an informal review process that is supposed to identify the strengths and weaknesses of the data and the possible regulatory alternatives. Bureau of Foods is responsible for scientific evaluation. If cancer is involved, the Division of Toxicology begins the review. The study is then forwarded to the Cancer Assessment Committee. If the Committee members feel that a substance has major scientific, economic, and regulatory significance, they will recommend formation of an interagency working group (IAWG) to evaluate scientific merit.

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2. Credibility of assessments.

Assessments were done by four different groups: The Ad Hoc Working Group, a Bureau of Foods Task Force, the Interagency Working Group, and the NAS.

The credibility of the initial assessment was low. Scientists within the agency who normally review such data and who were not involved in the review of nitrite felt uncomfortable with the caliber of individuals reviewing the study. Subsequent review of the study revealed many flaws in the data, casting further doubt on the conclusions drawn in the original assessment.

The credibility of the second review was not a major issue as this was an internal document looking at the broader issues of nitrosamine formation as well as nitrite carcinogenicity.

The final results of the IAWG deliberations were released two years after its review began. These results were supported by an independent pathology review. Thus, it had more credibility than the first assessment.

The findings of the NAS Committee on Nitrite have been largely accepted.

3. What was the extent of diversity of policy orientations within the assessment group? Outside pressures? Impact of pressures?

Since the Ad Hoc Working Group was composed entirely of FDA staff chosen by the Commissioner, it seems reasonable to assume that a similar “policy orientation” was shared by the members of this group. The Working Group's deliberations were not conducted in an open, public manner. Instead, their proceedings were kept secret, even from other FDA personnel, because of the importance of the issue and the fear of premature release of information. Thus, outside input into the process was minimal and special interest pressures would not have come into play. However, the Working Group was very much aware of the implications of their decision which would affect a $12-billion/yr industry and this fact, along with the knowledge that nitrite protects against another risk--botulism, most certainly affected the final approach suggested by the Task Force.

4. What were the time and resources necessary to complete the risk assessment?

The first assessment took two months.

The second assessment by the IAWG took from August 1978 to March 1979 to complete initial review and arrange for outside pathology review. The results of that review were available in August 1980 and a final report of IAWG was issued August 15, 1980. Cost of this review was approximately $900,000. The total time required for the second assessment was two years.

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The NAS report took 18 months to complete and cost approximately $500,000.

5. Responsiveness of the assessment agenda to public concerns, interest group concerns, professional concerns, and emergence of new scientific information.

The decision to form an Ad Hoc Working Group actually stemmed from the Commissioner's previous experience with the proposed saccharin ban, i.e., it reflected an agency awareness of public concerns and the importance to consider alternative regulatory actions. The subsequent appointment of an Interagency Working Group resulted from questions raised by FDA scientists concerning the carcinogenicity data used to support the agency's regulatory position.

6. Ability of the risk assessment to identify research needs.

Although the director of the Bureau of Foods presented recommendations for additional research to clarify some of the uncertainties in Newberne's data, the FDA commissioner's judgment was that no additional research was necessary. Thus, the first assessment does not identify areas where further research might clarify the issue. Later assessments did address this issue to varying degrees; for example, the assessment done by the NAS does address this issue rather extensively.

7. Extent to which risk assessment impeded or facilitated regulation.

This is a confusing question because regulation was inappropriate in this case. So, if the question is reworded to “impeded or facilitated making the most correct (or defensible) policy decision” I would answer that the assessment done by the Ad Hoc Working Group did not result in the appropriate policy decision while the assessment done by the IAWG did. The recently released NAS review of nitrite would concur with this conclusion.

8. Were related risk assessments consistent?

No. (This question was addressed earlier.) Assessments done by different groups led to different qualitative and quantitative conclusions. That is, the Ad Hoc Working Group concluded that nitrite was a carcinogen, as did the Bureau of Foods Task Force; however, the risk estimates of these two groups differed by tenfold. The IAWG concluded that nitrite was not carcinogenic, as did the NAS Committee on Nitrites.

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9. Was there a distinction between the weights given to science and policy considerations?

Some observers of the nitrite decision would suggest that policy considerations were weighted more heavily than scientific considerations in the initial assessment done by the Ad Hoc Working Group. Certainly, the makeup of the Group would indicate that the "policy-types" out numbered (and outranked) the scientists included in the group.

10. Mode and frequency of communication between assessors and regulators.

In the Ad Hoc Working Group, the assessors and the regulators were separated into two subgroups. The working group met frequently during the two-month period. In addition, the chief counsel did review and comment on the scientific report, suggesting that there was some interplay between two subgroups.

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ASBESTOS

William M. Stigliani

PART I: ENVIRONMENTAL PROTECTION AGENCY'S ASSESSMENT OF ASBESTOS-CONTAINING MATERIAL IN SCHOOLS

A. BACKGROUND AND CONTEXT

1. Describe the chemical and its uses.

Asbestos is a general term for a group of naturally occurring hydrated mineral silicates that separate into fibers. Asbestos minerals used commercially include: chrysotile, amosite, crocidolite, tremolite, actinolite, and anthophyllite asbestos.

Since asbestos is highly resistant to heat, has high tensile strength, and moderate to good chemical resistance, it has many uses. These include asbestos-cement pipe, asbestos paper, friction products, vinyl asbestos floor tile, paints, coatings and sealants, and gaskets and packings.

NOTE: This case study describes assessment procedures and issues and interpretations raised by others, but it is not intended to present independent positions or interpretations on either scientific or policy matters. The case has been reviewed by individuals outside the study project who are directly familiar with the federal analyses and decisions described; however, responsibility for the paper rests with the author, and it does not necessarily reflect the judgment of the Committee on the Institutional Means for Assessment of Risks to Public Health or the National Research Council. It has not been subjected to internal review procedures that apply to reports prepared by NRC committees.

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2. Describe how the question of risk was elevated to the agency agenda.

Warnings about health hazards in schools had been raised from several sources during the 1970s. Dr. William Nicholson and a team of Mt. Sinai scientists in a 1978 study did measurements in schools in New Jersey showing high levels of asbestos exposure. At the same time, the Public Health Service had issued an advisory concerning the hazard of asbestos in schools.

Subsequent to these warnings, the Environmental Defense Fund (EDF) petitioned the EPA, through section 21 of the Toxic Substances Control Act, to take regulatory action. The petition was denied, and EDF sued the EPA. In an agreement settled out of court, EPA agreed to proceed with rulemaking. The rule became final June 28, 1982.

3. Under what statutes and agency jurisdiction does the chemical fall? What statutory tests governed the decision?

The rule falls under the jurisdiction of section 6(a) of the Toxic Substances Control Act, which authorizes the Administrator to issue warnings and notification if a hazard exists.

The rule requires the governing officials (e.g., superintendent, head of school board, headmaster) to inspect all public and private primary and secondary schools in the U.S.A. for friable materials. If such material is found, three samples must be analyzed for asbestos by polarized light microscopy from an EPA recommended laboratory. If asbestos is found to be present in these samples, a school must: (1) notify the PTA, (2) notify all employees, (3) post notices in administrative areas, (4) give guidance for reducing asbestos exposure to maintenance people and (5) keep records of all correspondence (laboratory information, letters to employees, PTA, etc.).

4. What was the decision schedule? Note any statutory or other action deadlines.

Advance notice of proposed rulemaking	September 1980
First draft support document assessing risk of asbestos in schools	Oct. 1980
Final Rule	Feb. 1981 (postponed)

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Second draft support document assessing risk of asbestos in schools	July 1981
Final version of support document assessing risk of asbestos in schools	January 1982
Final Rule	June 28, 1982
Final date of compliance to rule	June 28, 1983

C. QUANTIFICATION AND CHARACTERIZATION OF RISK TO HUMANS (Sections B and C have been combined.)*

1. What health endpoints were evaluated?

Lung cancer, pleural and peritoneal mesothelioma, cancers of the larynx, oral cavity, esophagus, stomach, colon, and kidney.

2. What were the key data available for review? (What additional data were sought?)

Human Data

The epidemiological data selected to be the basis for making quantitative estimates of premature death from exposure to asbestos in schools was a large study of asbestos insulation workers (12,051 men) reported by Hammond et al. (1) and Selikoff (2). Various other epidemiological studies were considered but EPA decided the insulation workers study was the best one available. Several reasons were cited for this preference:

(1) the large sample size;
(2) the reasonableness of the estimates of asbestos exposure levels;
(3) detailed information on various cancer types;

* This section describes the second draft support document (July 1981). The final version of the support document (January 1982) is not discussed here since it contains no quantitative estimations of risk; the estimates calculated in the second draft were deleted.

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(4) verification of death certificates with supplemental information (e.g., autopsy reports, histological specimens) to detect misdiagnosed mesothelimas;
(5) appropriateness of the control group; and
(6) similarities between the material to which the insulation workers were exposed and the asbestos present in schools.

Data on Exposed School Population

EPA gathered information on the presence of friable asbestoscontaining materials in public schools and the number of people exposed by conducting a survey of the nation's school districts. There was about an 8% response rate. EPA subsequently contacted school districts that did not respond initially for further information.

Exposure Assessment

The prevalent exposure levels in schools containing friable asbestos materials were estimated based on data from a study by Sebastien et al. (3) of several buildings in Paris. EPA's reasons for choosing this study were the following:

(1) the areas and materials studied are similar to those in U.S. schools;
(2) the measurements were made by transmission electron microscopy (the only technique which is accurate for environmental sampling at low concentration); the measurements were checked by statistical quality control techniques, and the samples were taken over relatively long time periods; and
(3) comparisons were made with outdoor air and with a significant number of buildings that did not contain asbestos materials.

EPA felt other studies of U.S. schools did not meet these criteria. However, other studies were used to verify that the results of the Sebastien et al. study were consistent with data for U.S. buildings.

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3. Who performed the initial analysis? (What was their background? Available analytic resources?)

Two staff members of the Health and Environmental Review Division of the Office of Toxic Substances at the EPA performed the initial analysis. One was a Ph.D. epidemiologist; the other had an M.P.H. degree.

4. To what extent were results presented quantitatively? What factors influenced the degree of quantification?

The results were presented in a precisely quantitative fashion--as lifetime risk and number of premature deaths for students and adult employees.

The EPA staff felt there was sufficient data, with reasonable assumptions, to proceed with a highly quantified assessment.

5. How was uncertainty described in reaching final interpretations? Were crucial assumptions made explicit?

Uncertainty was described in two important ways. First, utilizing a linearized dose-response curve, EPA calculated a range of risks for school occupants, characterizing this range as low, intermediate and high. The range was based on high, low, and most likely predictions of three parameters:

(1) The cumulative exposure of insulation workers in the underlying study;
(2) The cumulative exposure of occupants of schools; and
(3) Mortality rates among insulation workers (based on observed deaths, and deaths calculated from uppper and lower 95% confidence limits).

Second, EPA considered the possibility that risk could be described by other dose response models, including the threshold model. The document states:

> EPA's policy is to select curves that cannot be ruled out on the basis of pharmacokinetics or poor “fit” to available dose-response data and that display the full range of reasonably possible increases in risk....EPA is unaware of information about the pharmacokinetics of asbestos that would enable the shape of a dose-response curve to be

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> inferred....It should be noted, however, that a curve could be developed to yield virtually any prediction of risk between zero and the level of risk predicted by the one-hit model or linear regression.

All crucial assumptions in describing these uncertainties, were explicitly stated.

6. How were qualitative factors dealt with?

- Mechanism of action, associated thresholds
- Effects on population subgroups
- Other confounding factors

EPA was unaware of information about the pharmacokinetics of asbestos that would provide definitive evidence about the shape of the dose-response curve, or the existence of thresholds.

EPA did consider biological susceptibility to asbestos as a function of age. After reviewing the literature, EPA determined that there was little confirmatory evidence to assume that children were more susceptible to asbestos exposure than adults. EPA made the assumption that annual incidence rate is not affected by age at first exposure. The longer remaining life expectancy of children compared with that of adults was the only factor that was incorporated into the quantitative risk estimate.

EPA did consider the greater risk of lung cancer from asbestos exposure among smokers. Data for the smoking-asbestos interaction was incorporated into the risk assessment.

The effect of fiber size and type on carcinogenic response was considered. Experimental evidence strongly suggests that fibers of certain sizes that reach the pleura, regardless of chemical composition, are more potent in producing mesothelioma than fibers of other sizes. EPA assumed that its use of data from the study of asbestos insulation workers avoided any major uncertainties that might otherwise have been presented by this finding. Because there were no data indicating that the fiber types or sizes to which the insulation workers were exposed were substantially different from those present in schools, the types and sizes in both settings were assumed to be similar.

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7. What qualitative factors affected the weighting of data? Were such criteria explicit and in accord with any general guidelines?

The calculated risk estimates were based on a linear, nonthreshold dose-response curve. EPA acknowledged that these estimates were conservative with respect to other models that could have been used, particularly the threshold model. EPA stated that "the existence of a threshold is theoretically possible but not demonstrated." EPA cited evidence, primarily in the form of mesothelioma case reports, that nonoccupational levels of exposure, perhaps as low as those found in schools, are sufficient to elevate risk. Other reasons cited by EPA for use of the linear model were: the fact that the authors of two major studies of asbestos workers believe their data for increased respiratory cancer risk are best described by the linear nonthreshold relationship, the fact that reviewers of the asbestos literature have recommended the use of this dose-response curve for low-dose extrapolations, and that for quantitative risk assessments of carcinogens in general, the EPA Interim Guidelines (EPA 1976, Albert et al. 1977) calls for the use of the linear nonthreshold dose-response curve.

As another issue EPA stated that peak exposures were not included in the risk assessment because their frequency could not be estimated. However, "for some individuals, custodians and maintenance workers in particular, the impact of peak exposures might dwarf the effect of exposure to prevalent asbestos concentrations....Custodians could easily double their cumulative exposure by spending less than 3 minutes per day dry sweeping....Viewed in this manner, the inability to incorporate peak exposures into the risk assessment may underestimate custodians' exposure (and therefore risk) by more than an order of magnitude."

EPA estimated that 6% of the exposed school children were smokers, and subject to the interaction between smoking and asbestos in the elevation of lung cancer risk. This estimate assumes that interaction will not take place in exposed students who become smokers after leaving school. If the interaction actually does occur, then the risk to school children predicted by EPA could be significantly underestimated.

Another assumption was that the estimate of premature death when only 16% of the workers have died (observation period of the cohort study) will be the same when all 12,051 have died. This assumption may underestimate the risk.

In calculating the cumulative exposure of the insulation workers, EPA assumed an induction period 10. Therefore, only exposures 10 years prior to the beginning of the observation period were considered "wasted." There is convincing evidence that the induction period may be longer, perhaps 20. Thus EPA may have overestimated the cumulative exposure, thereby under-estimating the risk at a given cumulative exposure.

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8. Describe any internal, internal-advisory (e.g., EPA's SAB), and external (e.g., NAS) scientific review of the initial analysis. What, if any, criticism was incurred?

In early 1980, a draft risk assessment was reviewed by four outside medical authorities. In the proposed rule (September 1980), public comments regarding health risks were solicited. In November 1980, there was a public rulemaking hearing in which comments were invited. In December 1980, there was a meeting with the Toxic Substances Subcommittee of the EPA's Science Advisory Board (SAB) to evaluate the risk assessment document.

The SAB raised the issue of the lack of definitive scientific evidence for choosing one dose-response curve in preference to another. They suggested that the risk assessment incorporate several different extrapolations. They also urged the authors to incorporate more evidence from qualitative epidemiologic data showing the incidence of mesothelioma occurring at extremely low levels of asbestos exposure. This data they suggested was the best evidence that a threshold did not exist. The SAB also suggested that more emphasis be given to peak exposures, which they believed caused an inordinately high risk to school maintenance workers. Finally, they strongly urged the EPA to incorporate the separate effects of asbestos exposure on smokers and nonsmokers into the risk assessment.

9. How were the issues raised in the review(s) accommodated?

In the revised draft (July 1981) EPA included a more extensive discussion of different dose-response models. In particular, EPA focused on the question of a threshold response to asbestos exposure. EPA did not dispute its possible existence, but presented information that would argue against such a contention. In particular, the revised risk assessment included more comprehensive documentation of cases of mesothelioma occurring after only short periods of exposure to asbestos.

The revised draft also discussed the importance of peak exposures. Although these were not factored into the risk assessment, EPA acknowledged the possible great underestimation of risk due to this omission (see Q. C. 7).

Data on asbestos exposure among smokers and nonsmokers was made available to EPA, and this information was incorporated in the revised risk assessment. The new data lowered the estimated risk since the incidence of smoking among school children is much lower than the incidence among insulation workers.

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10. What other issues arose concerning scientific data and their use? Briefly describe dissenting opinion.

Representatives from the Asbestos Information Association (AIA) also attended the December 1980 meeting. At that time the AIA argued that:

(1) the exposure data was taken from only one French study which was not representative of all the schools in the U.S.;
(2) there was no evidence that a threshold did not exist, and therefore a scientifically valid risk assessment could not be made until the issue was resolved; and
(3) the risk assessment was seriously flawed because no attempt was made to separate out the effect of smoking in the analysis.

11. Is the substance subject to past or possible future regulatory actions in other programs? If so, did the program office co-ordinate with other agencies or programs?

The Air and Water Offices at EPA each have established standards for asbestos. Also, OSHA, CPSC and FDA have all promulgated rules, pertaining to various aspects of asbestos use. Asbestos is subject to future regulatory actions or revision of current standards in each of the four agencies.

There was an asbestos working group established by the Interagency Regulatory Liaison Group to coordinate activities under the Carter Administration, but this group was disbanded in September 1981.

D. INTERPRETATION

1. What role did risk assessment have in the final agency document where standards were established to control the chemical?

The quantitative risk assessment played no identifiable role in the final rule. In fact the calculations and estimation of numbers at risk were removed from the final risk assessment document.

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2. Were there variations--over time or across agency programs--in the assumptions used? Were these variations significant to the final risk assessment?

By the spring of 1982, EPA, CPSC and OSHA all had developed (draft) quantitative risk assessments. The author of this case study compared the values of premature deaths quoted in these draft reports (standardized to an accumulated exposure of 2 fibers/cc, 20 years, 40 hours/week). Specifically, the calculated risks, in premature deaths per 1,000 were:

OSHA*	$\frac{8-260}{1,000}$
EPA	$\frac{57-348}{1,000}$
CPSC	$\frac{19-338}{1,000}$

It thus appears that there was significant agreement among the agencies in the calculation of risk from asbestos.

3. To the extent there were issues/concerns about questions of science, would the outcome have been improved by:

- A better system of in-house scientific review?
- Review by an outside scientific organization?
- Coherent federal guidelines on carcinogenic risk assessment?
- Better agency guidelines on the performance of risk assessment?
- Improved agency decision procedures?

The calculated numbers for school occupants at risk, present in the July 1981 draft, were deleted in the final version of the risk assessment (January 1982). Apparently, the decision to remove the numbers was made by the Deputy Assistant Administrator for Toxic Substances without consultation with the Toxic Substances Subcommittee of the EPA's Science Advisory Board (SAB).

* OSHA's estimates were quoted with no supporting information provided (FR. Jan. 13, 1982, 1807).

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(For the role of the SAB, see Q. C. 8). There were reports of concern among the SAB members, that the deletion and the bypassing of the advisory panel could reduce the credibility of EPA risk assessments. This break in communication may have been averted had established procedures on the role of the SAB in individual risk assessments been better formulated.

E. PERFORMANCE CONSIDERATIONS

1. Ability to obtain relevant scientific information.

EPA staff probably utilized the best scientific data available to them at the time the assessment was made. The major gap in information was lack of good comprehensive exposure data for U.S. schools.

2. Credibility of assessment; likelihood that interested parties would accept them as definitive.

The draft risk assessment (July 1981) is credible only to the extent that a nonthreshold linear low dose extrapolation is deemed to be credible. EPA staff was following EPA policy and guidelines in use since the mid-1970s. Since the choice of a model is based in part on a policy decision and not on complete scientific knowledge, some interested parties, quite predictably, attacked the use of the model.

3. What was the extent of diversity of policy orientations within the assessment group itself? What was the degree to which interest pressures could be exerted from outside the assessment group? What was the responsiveness of the assessment to these diverse interests?

The assessment group was made up of staff from EPA's Health and Environmental Review Division of the Office of Toxic Substances. The SAB, which played a key role in reviewing the document, was made up of academicians and various medical experts. None of these appeared to have any direct association with the asbestos industry. Early in the review process, representatives from the Asbestos Information Association (AIA), an industry trade association, expressed strong opposition to various aspects of EPA's quantitative risk assessment (see Q. C. 10), and voiced their objections on numerous occasions.

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After completing of the second draft of the quantitative risk assessment (July, 1981), the Deputy Assistant Administrator for Toxic Substances asked the assessment group to remove the calculated numbers of school occupants at risk from the risk assessment. The final version of the support document (January 1982) reflected this deletion. This change was done apparently without prior consultation with the SAB, and was reported to have had the wholehearted support of the AIA. Some interested members of Congress have harshly criticized the deletion, citing evidence that EPA officials consulted only the AIA before making the change. See also Q. D. 3 and Q. E. 7.

4. What were the time and resources necessary to complete the risk assessment?

Three to three and one-half person years was needed to complete the risk assessment.

5. Responsiveness of assessment agenda to public concerns, interest group concerns, professional concerns, and emergence of new scientific information.

This question has been answered in Questions A.2, C.8, C.9, and E.3.

6. Ability of the risk assessment to identify research needs.

An exposure study of asbestos in Houston schools was undertaken. This was done in part to answer the criticism incurred when EPA used data from a Parisian building as the basis for an exposure assessment. The Houston data, in fact, provided numbers that were quite similar to those obtained in Paris.

7. Extent to which risk assessment impeded or facilitated regulation?

Initially EPA was planning to require school districts to take corrective actions to protect occupants of schools from asbestos exposure. Such a rule would have been very expensive to inact. Under the Toxic Substances Control Act (TSCA), the cost of implementing a rule must be balanced by the benefits accrued from it. Thus, it would have been necessary under TSCA, for EPA to demonstrate that the health risk was sufficiently great to merit such action. A quantitative risk assessment probably would have been helpful to illustrate the number of lives that could be saved by the action. Also, other actions limiting the use of asbestos were being contemplated by EPA. It was under this perception, that EPA proceeded with the quantitative risk assessment, believing that it could be useful for a number of contemplated regulatory actions.

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The final asbestos rule dealt only with identification and notification of the presence of asbestos in schools. The rule requiring school districts to take corrective action was abandoned by EPA in April 1981. The Deputy Assistant Administrator (DAA) for Toxic Substances, who called for the deletion of the quantitative risk assessment from the July 1981 draft, cited two reasons for doing so. One was that the cost of the identification and notification rule is "very little", and thus a detailed quantitative risk assessment to support the rule was not needed. Secondly, it was important "to get the rule out." Controversy over the quantitative risk assessment was holding up progress.

The asbestos industry, which was not opposed to the identification and notification rule per se, was quite opposed to the quantitative risk assessment supporting the rule, and its promulgation.

Some members of Congress disagreed with the DAA's judgment. For example, the chairman of the House subcommittee on labor standards felt that without the numbers, the "sense of urgency" in implementing the rule is lost for local officials, parents and school employees.

8. Were related risk assessments consistent?

See Q. D. 2.

9. Extent to which there is an explicit distinction between weights accorded to scientific factors and policy factors.

The July 1981 draft made very explicit distinctions between scientific and policy factors utilized in the quantitative risk assessment. The distinctions were particularly clear regarding the use of dose-response models. See also, Q. C. 5 and Q. C. 7.

10. Mode and frequency of communication between assessors and regulators.

There appears to have been some problem of communication between the regulator and the assessor. See Q. D. 3 and Q. E. 3.

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ASBESTOS

PART II: OCCUPATIONAL SAFETY AND HEALTH AGENCY/NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH

A. BACKGROUND AND CONTEXT

1. Describe the chemical and its uses.

Asbestos is a general term for a group of naturally occurring hydrated mineral silicates that separate into fibers. Asbestos minerals used commercially include chrysotile, amosite, crocidolite, tremolite, actinolite, and anthophyllite asbestos.

Since asbestos is highly resistant to heat, has high tensile strength, and moderate to good chemical resistance, it has many uses. These include asbestos-cement pipe, asbestos paper, friction products, vinyl-asbestos floor tile, paints, coatings and sealants, and gaskets and packings.

2. Describe how the question of risk was elevated to the agency level.

By the late 1960s, extensive scientific documentation lead to widespread awareness and concern regarding the dangers of asbestos to workers. The Organization of Chemical and Atomic Workers (OCAW) union was publicly critical of what it perceived as flagrant industry violations of good industrial hygiene practices, as indicated by the American Conference of Governmental and Industrial Hygienists standard of 12 fibers/cc.

The asbestos issue had clearly come into the political limelight by 1970. During congressional discussions of the Occupational Safety and Health (OSH) Act, asbestos was highlighted on both floors of Congress as a primary example of the kind of hazardous exposure from which workers needed protection.

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Asbestos was included in the initial promulgation of Occupational Safety and Health Administration (OSHA) standards on May 29, 1971, a month after the agency came into existence. At that time, an exposure limit was set at 12 fibers per cc or 2 million particles per cubic foot of air. A petition for an emergency temporary standard to control concentrations of asbestos dust at more stringent levels was submitted to the Secretary of Labor by the Industrial Union Department (IUD) of the AFL/CIO on November 5, 1971. As a result of that petition, an emergency temporary standard of 5 fibers per cc of air was published by OSHA on December 7, 1971. This was followed on January 12, 1972, by OSHA's publication in the Federal Register of a “notice of proposed rulemaking” (NPRM) for a permanent standard of 5 fibers per cc.

On January 24, 1972, OSHA established an Advisory Committee on Asbestos Dust and charged its members to make recommendations with regard to the proposed standard. A criteria document on asbestos, which contained recommendations for a permanent asbestos standard, was submitted by the National Institute for Occupational Safety and Health (NIOSH) to OSHA on February 1, 1972. NIOSH recommended a 2 fiber per cc permissible level of exposure, to become effective two years after promulgation of a permanent standard. On February 25, 1972, OSHA's Advisory Committee on Asbestos Dust, by narrow margin, endorsed the NIOSH recommendations. OSHA held public hearings during the period March 14-17, 1972, to receive data, views, and arguments from interested parties concerning the proposed asbestos standard. A “permanent” standard for occupational exposure to asbestos dust was published in the Federal Register on June 7, 1972. The regulation established a permissible occupational exposure level of 5 fibers (longer than 5 micrometers) per cc of air, which was to be lowered to 2 fibers per cc after four years.

Less than two months after promulgation of the standard, the IUD of the AFL/CIO, along with other unions, filed suit (July 28, 1972) in the U.S. Court of Appeals challenging the regulation. Among other allegations, it charged that OSHA's decision to delay implementation of the two-fiber exposure limit for four years (until July 1, 1976) violated “highest degree of health protection” under section 6(b)(5) of the OSH Act.

On April 15, 1974, a three-judge panel in the U.S. Court of Appeals for the District of Columbia ruled in the case, in effect, denying the IUD petition but ordered OSHA to:

- Review the 1976 implementation date for the two-fiber exposure level requirement, suggesting that OSHA might require the two-fiber level in those sectors of the industry where it was already feasible to achieve; and

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- Provide a longer period for the retention of personal and environmental monitoring records. (The standard, as promulgated, provided for a three-year retention period.)

In response to the court-remanded issues, OSHA elected to initiate rulemaking. As indicated in the October 9, 1975 Federal Register notice:

> It is OSHA's belief that the record of the 1972 asbestos standard proceeding is inadequate to properly resolve the the two issues raised by the court's remand and that in the interest of achieving the best feasible occupational health protection a new rulemaking proceeding should be initiated so that fresh and more detailed evidence may be developed regarding changes in industrial usage, compliance capabilities, and employee health practices which have occured since the Standard's promulgation over three years ago.

In not taking any action earlier and then deciding to initiate a new rulemaking, OSHA effectively prohibited application of the two-fiber standard prior to July 1, 1976.

The NPRM went beyond the court-remanded issues and addressed several others. In addition, it called for lowering the standard of exposure to 0.5 fibers/cc with a ceiling of 5 fibers/cc for any period not exceeding 15 minutes. There was no discussion of when or if the proposed 0.5-fiber standard would be feasible.

Closing date for comments on the 1975 proposal was extended twice and ended up at April 9, 1976. In the meantime, on December 1, 1975, OSHA requested that NIOSH reevaluate the health effects data on asbestos. A revised criteria document was prepared and completed in December, 1976. The NIOSH recommendation stated that the asbestos standard should "be set at the lowest level detectable by available analytical techniques." NIOSH defined this level as 0.1 fibers per cc.

As far as could be determined, no further action was ever taken on the 1975 NPRM. Hearings were never held.

3. Under what statutes and agency jurisdiction does the chemical fall? What statutory tests governed the decision?

The chemical falls under the jurisdiction of the Occupational Safety and Health Act of 1970. The 12 fibers/cc standard was promulgated under Section 6(a) as a "consensus standard" not requiring any rulemaking. The "emergency temporary standard" of 5 fibers/cc was promulgated without rulemaking under Section 6(c). The "permanent standard" of 5 fibers/cc (lowered to 2 fibers/cc after four years) was promulgated under Section 6(b). Rulemaking is required for permanent standards, and the standard should be stringent enough to provide total worker protection for 30 years of exposure to the extent feasible based on latest information. Section (20) calls for NIOSH to produce criteria documents with recommendations that protect the worker for 30 years based on health considerations alone.

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4. What was the decision schedule? Note any statutory or other action deadlines.

Action	Date
Initial promulgation of OSHA 12 fibers/cc standard	May 29, 1971
Emergency temporary standard of 5 fibers/cc published as result of AFL/CIO petition	Dec. 7, 1971
NPRM for “permanent” 5 fibers/cc standard	Jan. 12, 1972
NIOSH submits Criteria Document to OSHA	Feb. 1, 1972
Final rulemaking for 5 fibers/cc standard which would be lowered to 2 fibers/cc on July 1, 1976	June 7, 1972
AFL/CIO suit challenging four-year delay of 2 fiber/cc implementation	July 28, 1972
Court remand to OSHA to review the 1976 2 fibers/cc implementation date	April 15, 1974
OSHA initiates new rulemaking (NPRM) in response to court's remand	Oct. 9, 1975
NIOSH submits Criteria Document to OSHA	Dec. 1, 1976

C. CHARACTERIZATION OF RISK TO HUMANS (Sections B and C were combined.)

1. What health endpoints were evaluated?

1972 NIOSH Criteria Document

Primary emphasis was on asbestosis, with some consideration of bronchogenic cancer and mesothelioma.

1976 NIOSH Criteria Document

Emphasis was on mesothelioma, lung and gastrointestinal cancers.

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2. What were the key data available for review? (What additional data were sought?)

1972 NIOSH Criteria Document

The British Occupational Hygiene Society (BOHS) study of asbestosis incidence in British factories was the chief document used in the development of the asbestos standard. Numerous epidemiologic studies dealing with lung cancer and mesothelioma incidence were also reviewed.

1976 NIOSH Criteria Document

Various epidemiologic studies for lung cancer, cancer of the G.I. tract, and mesothelioma were evaluated. References are listed on pp. 88-91 of the document. Also, a paper by Schneiderman (1974) which critiqued two recent papers (McDonald, 1973, and Enterline et al. 1973) was influential. The two papers in question supported the idea of a threshold level for asbestos cancer induction. Schneiderman concluded that these data did not provide evidence for a threshold or for a "safe" level of exposure.

3. Who performed the initial analysis? (What was their background? Available analytical resources?)

1972 Criteria Document

The initial analysis was performed by four NIOSH staff scientists. No data are available on their areas of expertise.

1976 Criteria Document

The analysis was performed by two staff scientists. One had training in epidemiology and toxicology. The other was trained in epidemiology and industrial hygiene. The latter did the analytical chemistry analysis in the document.

4. To what extent were results presented quantitatively? What factors influenced the degree of quantification?

1972 Criteria Document

In the BOHS study, data on 290 asbestos workers were fitted to a dose-response curve and the conclusion was drawn that an accumulated exposure of 100 fiber-years/cc (2 fibers/cc for 50 years) would reduce early clinical signs of asbestosis to less than 1%. The NIOSH standard was directly based on this study,

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assuming a 30-year worklife; i.e., 3 fibers/cc for 30 years. Introducing a "measure of prudence" factor to account for carcinogenicity, the standard was lowered to an average exposure of 2.0 fibers/cc.

1976 Criteria Document

NIOSH concluded that "evaluation of all available human data provides no evidence for a threshold or for a 'safe' level of asbestos exposure." Consequently, it was decided that the standard should be set at the lowest level detectable by available analytical techniques. No quantitative risk assessment was performed.

5. How was uncertainty described in reaching final interpretations? Were crucial assumptions made explicit?

1972 Criteria Document

A cancer "safety factor" was introduced by causing the standard to be reduced from 3 fibers/cc to 2 fibers/cc. No justification was given for choosing such a factor, and no data on cancer health risk to workers was estimated based on the new standard.

1976 Criteria Document

Uncertainty was not addressed. By 1976 NIOSH endorsed the non-threshold theory of cancer. The document states:

> There are data that show that the lower the exposure, the lower the risk of developing cancer. Excessive cancer risks have been demonstrated at all fiber concentrations studied to date. Evaluation of all available human data provides no evidence for a threshold or for a "safe" level of asbestos exposure.

6. How were qualitative factors dealt with?

In 1972, there were two schools of thought regarding research approaches toward the identification and characterization of asbestos related diseases. One school supported an epidemiologic protocol for determining asbestosis. The other focused on epidemiologic evidence of cancer. NIOSH gave most weight to the former approach in 1972. Cancer was considered to be an important effect, but OSHA/NIOSH supported the idea of a threshold value for cancer.

By 1976, cancer was considered to be the most important and serious effect. NIOSH supported the nonthreshold theory of cancer.

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7. What qualitative factors affected the weighting of data? Were such criteria explicit and in accord with any general guidelines?

The question of thresholds was key to the weighting of data (see Q. C.5 and Q. C.6). The threshold theory of cancer, maintained by NIOSH in 1972, was supported by a 1971 National Academy of Sciences (NAS) study which stated that "the appearance of a gradient of effect suggests that there are levels of inhaled asbestos without detectable risk." However, the Surgeon General of the United States twice (in 1968 and 1970) endorsed the nonthreshold concept for carcinogens.

The nonthreshold theory of cancer, maintained by NIOSH in 1976, was stated as NIOSH policy in May 1975. At that time, Dr. Fairchild, the Director of NIOSH, quoted the Surgeon General's 1968 statement in order to justify setting standards for carcinogens to the lowest feasible level.

8. Describe any internal, internal-advisory, and external scientific review of the initial analysis. What, if any, criticism was incurred?

1972 Criteria Document

The initial document was completed by NIOSH staff with input from selected outside sources. The document was reviewed externally by three research scientists and doctors familiar with asbestos-related diseases. The revised document was then reviewed by selected representatives of professional societies (e.g., American Occupational Medicine Association, American Industrial Hygiene Association). These reviewers were independently appointed by the societies they represented. The next level of review was an internal review by the Director of the Institute and other senior NIOSH staff. All comments from previous reviewers were organized into a table delineating which comments had been accepted and which rejected. The senior committee went over all the comments and the rationale for responding to them in a particular way.

The major criticism incurred dealt with NIOSH's focusing on asbestosis data rather than on the data dealing with cancer.

1976 Criteria Document

The review process was similar to that of the 1972 document. The 1976 document was based entirely on the premise that there was no safe level of exposure to asbestos. It has not been determined whether this position was critized during review. However, as of May 1975 the nonthreshold theory of cancer had been established NIOSH policy.

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9. How were issues raised in the review(s) accommodated?

1972 Criteria Document

A cancer "safety factor" was added after a standard was established based on asbestosis data.

1976 Criteria Document

See Q. C.8

10. What other issues arose concerning scientific data and their use? Briefly describe dissenting opinion.

Industry was highly critical of the 1976 document. Representatives stated that the NIOSH presented no dose-response information to demonstrate that any exposure to asbestos was unsafe.

11. Is the substance subject to past or possible future regulatory actions in other programs? If so, did the program office co-ordinate with other agencies or programs?

Asbestos is subject to possible regulatory action by EPA and Consumer Product Safety Commission. There was an asbestos working group established by the Interagency Regulatory Liaison Group to coordinate activities under the Carter Administration, but this group was disbanded in September 1981.

D. INTERPRETATION

1. What role did risk assessment have in the final agency document where standards were established to control the chemical?

The 1972 NIOSH criteria document played a key role in supporting the final OSHA rule establishing a permanent standard of 2 fibers/cc (FR, June 7, 1972). As described in Q. A.2, OSHA endorsed the NIOSH recommendation prior to issuing the rule.

It is hard to determine the role the 1976 NIOSH criteria document played in supporting the proposed rule establishing the 0.5-fiber/cc standard (FR, Oct. 9, 1975). It was published more than a year after the proposed OSHA rule and called for an even more stringent standard (0.1 fibers/cc). No further action on the proposed rule was taken.

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2. Were there variations--over time or across agency programs--in the assumptions used? Were these variations significant to the final risk assessment?

There were variations over time, but there was apparent consistency across agencies. In 1968 and 1970, the Surgeon General of the United States stated unequivocally that thresholds for carcinogens did not exist. In 1972, the NIOSH criteria document and an EPA rule for national emissions standards recommended or established exposure levels for asbestos consistent with a threshold value for asbestos carcinogenesis. In May 1975, Dr. Fairchild, the Director of NIOSH, quoted the Surgeon General's 1968 statement in order to justify setting standards for carcinogens to the lowest feasible level. At that time EPA Interim Guidelines (EPA, 1976, Albert et al. 1977) called for the use of the linear nonthreshold dose-response curve. These variations were significant to the final risk assessment as explained in previous questions.

3. To the extent there were issues/concerns about questions of science, would the outcome have been improved by coherent federal guidelines on carcinogenic risk assessment?

Federal guidelines could have established the scientific and policy bases for assessing cancer risk. Much of the confusion regarding statements about cancer thresholds, the use of data for asbestosis rather than cancer, and the use of a cancer "safety factor" may have been reduced. Implicit assumptions regarding science and policy questions may have become more evident.

E. PERFORMANCE CONSIDERATIONS

1. Ability to obtain relevant scientific information.

Senior officials at NIOSH in 1972 stated that cancer studies published up until 1972 were inconclusive and ambiguous. Air sampling studies had been performed by different methods which made intercomparison difficult. In the view of one official there may have been good unpublished data at that time. However, he stated that NIOSH adhered to a strict policy regarding new scientific information which may have precluded the use of this new data. The policy asserted that new information, which had not yet been published in open literature for public criticism, could only be included in the criteria document if it were peer reviewed. In the view of this senior official, scientists are often unwilling to allow such a peer review as it may spoil the opportunity to have their data published later.

By 1976, the body of information was much more extensive and readily obtainable.

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2. Credibility of assessments, likelihood that interested parties would accept them as definitive.

For the most part, industry was satisfied with a 5-fiber/cc standard as proposed by OSHA and as set by ACGIH, and did not dwell very much on health arguments. There was disgreement within industry with the argument that 2 fibers/cc was needed to protect the health of workers. Some claimed that there was no evidence for hazard at low levels since current and recent incidences of disease resulted from past exposures at far higher concentrations. This opinion was given further support in an industry-sponsored study by McDonald (1973) who claimed to have evidence that only high exposure caused cancer. By 1975, however, the 2 fibers/cc standard was widely accepted.

On the other hand, labor was very dissatisfied with the proposal of 5 fibers/cc. Mention was made of the fact that the British Occupational Hygiene Society suggested a level of 2 for chrysotile but 0.2 for crocidolite which is known to be associated with mesothelioma.

The Textile Workers Union wanted a standard that used engineering controls and good handling practices to push toward zero exposure. The AFL/CIO testified in favor of a more stringent standard than NIOSH had proposed in 1972 which was perceived as essentially an asbestosis standard. AFL/CIO pushed hard for a cancer standard. The 1975 NPRM and the 1976 NIOSH criteria document were more in line with labor's viewpoint.

On February 4, 1976, some 65 representatives from companies and trade associations representing manufacturers and processors of asbestos products in the United States participated in a meeting held in Washington, D.C. They overwhelmingly endorsed the 2-fiber level as attainable by application of engineering technology. However, they stated the proposed 0.5 fiber level was unnecessary, impracticable and lacked medical justification.

3. What was the extent of diversity of policy orientations represented within the assessment group itself? What was the degree to which interest pressures could be exerted from outside the assessment group? What was the responsiveness of the assessment to these diverse interests?

The group that wrote the 1972 criteria document were all NIOSH personnel. However, they received input from individuals representing quite diverse opinions. Dr. Selikoff, who had prepared a brief for labor for its 1971 petition to OSHA for an emergency temporary standard, contributed to the initial document. Industry oriented professional societies, such as the ACGIH, were invited to comment later in the review process. The incorporation of a cancer safety factor into the standard was probably in part a response to pressure from labor groups.

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It appears that there was little policy diversity among the groups that prepared the 1976 NIOSH document.

4. What were the time and resources necessary to complete the risk assessment?

1972 Criteria Document

In the opinion of one of the major architects of the document, 10-15 person years were needed in just the preparation and review. However, the criteria document covered more areas than a normal risk assessment. Guidance was given in air sampling methodology, medical surveillance requirements, labeling, protective equipment and clothing, and work practices.

1976 Criteria Document

In the opinion of one of the authors of the document, perhaps 1-1/2 person years were needed to complete the document. This document was not as extensive as the 1972 document and basically dealt with a review of the health effects, sampling methods, and the proposed standard.

5. Responsiveness of assessment agenda to public concerns, interest group concerns, professional concerns, and emergence of new scientific information.

This question has been answered in Questions A.2, E.2, and E.3.

6. Ability of the risk assessment to identify research needs.

A consensus of opinion among interviewed NIOSH personnel was that the risk assessment did stimulate research to some degree, but that the chemical was of such universal interest that the influence was probably minor.

7. Extent to which risk assessment impeded or facilitated regulation

The 1972 criteria document probably facilitated regulation by supporting the premise that there was a safe level of exposure and calculating what that exposure would be. It is difficult to determine the impact of the 1976 criteria document, since the proposed 1975 OSHA rule was not made final.

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8. Were related risk assessments consistent?

See Q. D.2.

9. Extent to which there is an explicit distinction between weights accorded to scientific factors and policy factors.

The asbestos example is a good one to illustrate the lack of distinction that can occur between scientific factors and policy factors. In 1972, NIOSH did not accept the premise that any level of exposure to a carcinogen was unsafe. An NAS study in 1971 supported this conclusion. A contrary opinion was voiced twice by the Surgeon General of the United States in 1968 and 1970. He stated that since there is no threshold level for a carcinogen, any level must be deemed to be unsafe. Indeed, OSHA, in 1971, referred to the Surgeon General's statement when promulgating its consensus standards. There is no documentation as to why NIOSH chose the NAS view over that of the Surgeon General.

By 1976, NIOSH had changed its position, treating cancers as nonthreshold substances. In fact, Dr. Fairchild of NIOSH justified this position in 1975 by quoting from the 1968 Surgeon General's statement.

10. Mode and frequency of communication between assessors and regulators.

There was frequent communication between OSHA and NIOSH during promulgation of the asbestos standards. OSHA officials were invited to peer review meetings, and a record of all review comments and responses was submitted to OSHA as part of the official record.

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AN ANATOMY OF RISK ASSESSMENT: SCIENTIFIC AND EXTRA-SCIENTIFIC COMPONENTS IN THE ASSESSMENT OF SCIENTIFIC DATA ON CANCER RISKS

Lawrence E. McCray

SUMMARY

A single risk management decision is often based on an assessment that, itself, comprises many discrete decisions--choices among assumptions, interpretations, relative weighting of conflicting pieces of evidence--that analysts must make if useful overall conclusions are to be reached concerning the existence or level of a cancer risk.

This paper attempts to identify common elements of risk assessment, to characterize these components individually, then to draw general inferences about the nature of risk assessment. The paper covers three areas:

- the inherent structure of risk assessment
- the relationship of scientific judgment and "value" judgment in risk assessment
- some implications for the organization and management of risk assessment

APPROACH

Regulation--and the rule of law more generally--demands simplification. The regulation of potential public health risks often demands simple categorical findings (for example, whether a particular chemical is carcinogenic or not). Regulation by its nature cannot easily tolerate ambiguities or cope with probabilities: it proceeds as if a "Simplification Imperative" is at work. A highway speed limit, for example, cannot reasonably be posted as "around 55 mph"; a speeding ticket cannot reasonably state that a driver "probably" was exceeding the posted speed.

NOTE: This paper was originally prepared for the use of the National Research Council's Committee on the Institutional Means for Assessment of Risks to Public Health. It is not intended to present independent positions or interpretations on scientific or policy matters. It does not necessarily reflect the judgment or position of the Committee or the National Research Council. It has not been subjected to the internal review procedures that apply to reports prepared by NRC committees.

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The assessment of a public health risk is inherently complex, and ambiguities and probabilities abound. Scientists consider many qualifying factors when contemplating a chemical's potential carcinogenicity. Gaps in data and knowledge are typically large.

Results that are conclusive enough to satisfy a scientist's professional standard of proof are rare. If public health risks are to be regulated at all, many assumptions--deliberate choices in the face of scientific uncertainty--must be made in order to satisfy a regulator's need for simplified answers to two questions:

- Is the substance carcinogenic or not?
- How does human risk vary with actual exposure to the substance?

This paper is an initial inquiry into the nature of those analytic choices--the inherent “components” of risk assessment.

The analysis identifies 36 distinct components*, which are listed in the attachment. The components fall into three analytically distinct activities: hazard identification, dose-response assessment, and exposure assessment. Hazard identification involves the qualitative determination of whether a particular agent causes a particular adverse effect in humans. Dose-response assessment describes how such effects are related to dose. Exposure assessment estimates the level of human exposure to the substance, with and/or without regulatory controls. A risk assessment, thus, combines a hazard identification or a dose-response assessment with an exposure assessment.

The 36 components are arrayed in the attachment according to these three activities, and, within each activity, according to the type of the available scientific data. Generally, we can classify these as: (1) human data, (2) animal bioassay data, and (3) data from other sources.

Fewer than 36 choices will be confronted in any one assessment; the actual number depends on the nature of the evidence that is available to be evaluated.

The list of components was originally generated by abstracting the issues covered in reviews of the scientific principles of carcinogenic risk assessment by the U.S. government's Interagency Regulatory Liaison Group and other organizations. Reviewers of early drafts of this paper were then asked to suggest additions to the list to make it a comprehensive accounting of the areas where discretion is applied in particular assessments.

* This list was later expanded to include 50 components. See Risk Assessment in the Federal Government: Managing the Process (National Academy Press, 1983) pp. 29-33.

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GENERALIZATIONS ABOUT THE NATURE OF DISCRETION IN RISK ASSESSMENT

A review of the 36 components leads to several general observations concerning the structure of risk assessment:

The components of risk assessment vary widely in form.

Some, for example, involve quite simple choices among a limited number of options:

Examples: Component 13 is the choice of a statistical confidence limit (the choice of 95% is conventional) that is used to classify bioassay results as "positive." Component 9 is the binary decision whether or not to count or to ignore benign tumors as positive results in bioassays.

Others are umbrella judgments that may incorporate a large number of scientific factors or an open-ended array of choices.

Examples: Component 4 addresses the scientific acceptability of an epidemiology study. Many factors affect this judgment--clearly, the list of potential flaws in designing or conducting epidemiology studies is long. This judgment must be applied for each available study.

Component 16 is an open-ended question of whether particular bioassay results should be discounted for purposes of hazard identification because the test animal's physiological response to the chemical is unique, and thus that its response does not reliably predict human responses. This list of possible scientific rationales for this kind of physiological extenuation is long, if not open-ended--including interspecies metabolic differences, pharmacokinetic differences, etc. It is doubtful that a checklist could be constructed that would cover all rationales.

Each assessment involves many mandatory choices.

Discussions of risk assessment policies for particular substances often reduce to debates over one or two scientific issues--typically, for example, the shape to be assumed for the dose-response function and/or whether or not to use upper confidence levels to define the dose-response curve. In truth, however, an analyst's discretionary judgments unavoidably enter an assessment at many points, whether or not they are explicitly presented and subjected to scrutiny. In fact 20 of the components normally require discretionary choices (whether implicit or explicit) for every quantitative risk assessment that involves both animal and human effects studies. The "Simplification Imperative" casts a wide net.

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Examples: Component 14 requires a judgment whether a particular bioassay is strong enough to be considered in hazard evaluation; the risk assessor must make this choice for each study encountered.

Component 35 covers the treatment of particularly susceptible populations: even a decision not to evaluate such susceptibles is a choice among analytic options, whether recognized or not.

If only animal data are available and a quantitative assessment is performed, 15 mandatory choices remain. For the hazard identification phase alone, 10 mandatory components present themselves (7 for bioassay data, 3 for human effects data).

The other 16 components come into play only under special circumstances.

Examples: Component 7 covers the case of weighting results of bioassays that used different routes of exposure than the one that is of primary regulatory concern (e.g., whether results from a stomach intubation study are relevant for airborne chemical exposures). This component does not come into play if all bioassays were inhalation studies.

Most of the components involve some form of weighting.

Twenty-eight of the components involve weighting decisions, many of which involve decisions about which facts, among a conflicting set of findings, are to be given consideration.

Examples: Component 6 covers the relative weights to be placed on positive and negative epidemiology results, when both are reported for a substance.

Component 26 treats the decision on whether to base dose-response assessment solely on results from the most sensitive bioassay treatment group; this may be expressed equivalently as "what relative weight should be given to results from different treatment goups in a bioassay?" One choice is to apply weighting values of one to response of the most sensitive treatment group and a value of zero to data from all other treatment groups. Another possible choice would be to apply equal weights, in effect averaging results across treatment groups.

Component 21 covers the "grand" weighting decision for hazard identification: what relative weights to apply all the results from human studies, bioassays, structure-activity considerations, and short-term tests to reach a final inference about cause-and-effect in humans.

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The other 8 components involve a choice among statistical criteria or a choice among alternative ways to express results.

Examples: Component 13 requires a decision about the statistical confidence level to be used to classify bioassay test results as "positive."

Component 24 requires a choice between using "best estimates" or "upper confidence limits" in characterizing the dose-response function.

The components of risk assessment appear to have varying levels of specificity--but for many, the level of specificity is somewhat unclear.

A question of interest in evaluating the advisability of generic guidelines for risk assessment is the level of generality at which discretionary judgment must be applied. The most specific components are those that apply to specific test results--e.g., a particular bioassay report. Midrange applications are those that apply to the risk assessment for a particular substance, but not across substances. A generic component involves judgment that could be applied across substances and, thus, across regulatory programs. The results of an attempt to classify components in this manner are inconclusive.

Three components (4, 14, 15) appear to be of the most specific variety; they apply to individual test results.

Example: Component 14 involves a characterization of the scientific acceptability of particular bioassays.

Five midrange components (16, 20, 21, 25, 31) seem relatively clearly to apply to the unitary risk assessment--that is, they apply to multiple data types for a particular substance, but not across substances.

Example: Component 16 weighs physiological extenuations for a particular chemical risk. These are typically based on an understanding of human metabolic pathways or pharmacokinetic factors specific to the chemical. Determinations for component 16 seem unlikely to generalize across chemicals.

Six components (5, 13, 19, 24, 30, 34) appear to be amenable to generic policy formulation. (Note: these components tend to the "value" end of the science-value spectrum discussed in the following section.)

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Example: Component 19 requires a definition of the statistical confidence level for defining positive short-term tests. Whatever that definition is, it seems reasonable to hold it constant across tested substances.

However, well over half of the components seem to resist easy classification.

Examples: Component 8 requires a decision about whether total body tumors or specific tumor types should be counted in bioassays. It is unclear whether this decision could be made generically or should remain flexible for chemical-by-chemical determination.

Component 7 requires decisions in assessing animal data in the case that the route of exposure in the study data is different from that of regulatory concern. Some rules of thumb may be desirable (e.g., don't rely too much on studies involving dermal exposures for assessing airborne human exposures), but some argue that there should be case-by-case evaluation of the question.

Component 28 requires choices among varying interspecies conversion factors in dose-response estimation. There are two or three dominant options, including those based on relative surface area and relative body weight. Some observers would oppose the choice of any one conversion factor as a generic policy, asserting that, for example, metabolic factors may require case-by-case variation.

It seems clear that there are limits to the extent to which risk assessments can be made uniform by the imposition of generic rules. There are many points in an assessment where scientific considerations unique to the substance under evaluation should be assessed.

Ten different fields of expertise are touched in the components of risk assessment; the field that is most pervasively relevant is biostatistics; many individual components require a blend of expertise; "concordance analysis" may be of strategic importance over the long term.

We have made an initial attempt to describe the major field of knowledge that is applicable for each component. The results:

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Field of Knowledge	No. of Components
Biostatistics	13
Carcinogenesis	11
Toxicology	10
Pathology	6
Epidemiology	4
Genetics	4
Medicine	3
Nutrition	2
Biochemistry	1
Teratology	1

One reason that biostatistics is pervasive is that many of the components require giving relative weights to findings from different studies or tests; this question turns on the relative power of the tests and relative strengths of association reported in test results.

For nearly half of the components, a blend of disciplinary backgrounds may be required:

Number of Scientific Fields Required	No. of Components
4	2
3	2
2	11
1	19
0	2
	36

Many of the components that rest on a single disciplinary field are found in the hazard identification phase of risk assessment; the need for multidisciplinary expertise is more common in the dose-response estimation phase.

These findings have implications for the administrative management of risk assessment. Because so many specialized fields may be directly relevant, it may prove difficult for agencies to engage experts on all the relevant fields in the units that conduct risk assessments, or for groups that review risk assessments to ensure that all relevant disciplines are represented.

Not listed among the standard fields of scientific knowledge is a unique "discipline" that has a bearing on choices for a number of components; we may call this discipline "concordance analysis" (some have suggested the term "risk assessment science" for the same concept). Concordance studies involve empirical reviews of the concordance between indicators of carcinogenicity revealed in lower species and known human carcinogenicity. This line of empirical inquiry is largely independent of any of the standard scientific disciplines.

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Examples: Component 18 requires judgment about the predictive power of particular short-term tests; confidence in such tests will be enhanced if concordance studies show them to be highly correlated with bioassay results, which in turn show some concordance with human carcinogenicity.

Component 12 requires a decision as to whether a bioassay should be considered positive if any single sex/dose/strain grouping is positive, or whether the results for other groupings should be factored in. Concordance studies could eventually address this issue by applying alternative decision schemes to available animal data on known human carcinogens and determining which scheme "predicted" the fewest wrong answers.

Components are better characterized for hazard identification and dose-response assessment than for exposure assessment.

Twenty-one of the components deal with hazard identification, and 10 more are concerned with dose-response estimation. Exposure assessment accounts for only two components (32, 33). This gives an impression that exposure assessment, at least in relative terms, is an ad hoc undertaking. There are two plausible reasons for this contrast. The first, and the most likely, is that exposure assessment procedures vary widely by type of exposure, with very few major analytic elements common to all routes of exposure: for example, an exposure assessment for a food additive may simply share few prominent assumptions/interpretations with an exposure assessment for a mobile source air pollutant. A second possibility is that a larger number of common components of exposure assessment are present, but they simply have not been recognized and developed because public attention and analytic focus have been devoted to questions of toxicology.

SCIENCE AND VALUE IN RISK ASSESSMENT

There has been much debate over whether risk assessment is "scientific" or "political" in nature, and, therefore, whether scientists or politically accountable officials should have the final authority in performing assessments. Familiar assertions in the current debate over risk assessment include these:

Risk assessment is inherently scientific in nature; it should be done in isolation from political influences, which can only distort true scientific judgment.

The basic problem in risk assessment is that political appointees in the agencies conceal their value judgments under the mantle of science.

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> The basic problem in risk assessment is that scientists conceal their personal value judgments in risk assessments with the mantle of science"; or, alternatively, "All scientific judgments must necessarily be made by scientists; however, not all judgments made by scientists are necessarily scientific.
>
> All risk assessments are inherently political. Since science cannot fully characterize carcinogenesis, there is no alternative but to apply value judgments in areas of scientific uncertainty.

As in most controversies, there is probably an element of truth in each of these conflicting observations. It is possible that the difficulty in understanding the relative role of scientific judgment and value judgment in risk assessment is that observers have addressed the question for the risk assessment process as a whole. The problem may be resolved by examining the question for the individual components of risk assessment.

Many observers believe that risk assessments involve a mix of scientific and extra-scientific judgments. This section reports an experimental attempt to address science/value questions for the several components of risk assessment. The central idea is to classify each of the 36 components as a "scientific" judgment, "value-based" judgment, or as an intermediate form. The exercise corresponds to a requirement of the FDA study contract.*

The experimental approach was to rate each component on a five-point scale ranging from "pure science" to "pure value." These ratings were supplied by scientists and social scientists who were knowledgeable about carcinogenic risk assessment and its uses in policy. The underlying premise--a naive one, in retrospect--was that segregating matters of science from matters of value might hold a key for the study of institutional means of risk assessment. Scientific components of a risk assessment, for example, might be left to an organization primarily responsive to scientific authority, while extrascientific considerations involving value judgment might be isolated and determined by individuals responsive to normal democratic processes--for example, political appointees in the regulatory agencies. The results scuttle any hopes for such a neat solution.

* "The process of risk assessment will be delineated in terms of its individual components, identifying and distinguishing those that are scientific in nature from those that are value judgments or policy. In addition, an effort will be made to identify and describe those components that are neither strictly science or policy but a hybrid consisting of elements of both."

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None of the components is purely scientific.

Reviewers characterized no component as "pure science."

Upon reflection, it became clear that this finding is tautological: the list of components had been constructed in a way that excluded consideration of purely scientific considerations. Clearly, there are very many matters of pure science in a risk assessment, for an obvious example, the term "pure science" would include the laws of addition. Addition is used in all risk assessments--and faulty addition would certainly affect the scientific merit of a risk assessment. However, because there appears to be scientific certainty--or at least consensus--about the laws of addition, the matter is not addressed in the materials (formal guidelines, case summaries) that served as the basis for identifying the 36 components.

A handful of components are seen as pure value judgments.

Six components (5, 24, 30, 32, 34, 36) appear to involve no scientific judgment.

Example: Component 5 requires a statistical threshold for considering human effects studies to be "positive." This choice rests on the value society places on avoiding false negatives -- e.g., can we accept 1 chance in 20 (or 1 in 100?) of falsely exonerating a harmful substance? Science cannot illuminate the answer to this question.

For the majority of components, reviewers see a mix of science and value--and they disagree widely on the proportion of the mix. Reviewers tend to define "scientific" as reflecting the degree of current scientific consensus.

For 30 of the components, observers characterized the item in the midrange between pure science and pure value. For 20 of the 30, there is serious disagreement (not obviously reflecting the general policy orientation or disciplinary training of the observer) about the proportions of the mix.

Example: Component 23 requires a choice (or choices) among mathematical models to extrapolate from high to low doses in animal studies. Some observers see this as "mostly scientific," emphasizing that the choice must be constrained by scientific considerations--like statistical goodness of fit in the observed range and biological plausibility in the low dose range. Others see the choice as "mostly value," claiming that scientific

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considerations merely narrow the range of sensible models (and noting the lack of scientific consensus in biological plausibility); this leaves the final selection open to value judgment. Further discussion between two such observers turns to the diffuse and metaphysical.

After averaging the ratings in cases where observers' ratings diverge, we find the array of general ratings "tendencies" for the 30 midrange components to be:

Mostly Scientific	7
(Intermediate)	9
Mixed	7
(Intermediate)	3
Mostly Value	4
	30

In general, components in the hazard identification phase of risk assessment are perceived as more "scientific"; 13 of the 21 components in this phase are listed in the first two categories. For dose-response assessment, only 3 of its 10 components are listed in these categories.

Although some of the components are judged to be "mostly scientific" judgments, even for these there is a margin of difference in opinions among scientists--one that makes the choice of scientist consulted an entry point for value considerations.

Example: Component 15 covers the pathology for bioassays. No one doubts that pathology should be left to qualified pathologists; however, there is some scientific variation in the way different component pathologists characterize the same results--a difference they perceive as based solely on scientific considerations, not personal values. However, the differences correspond to different levels of conservatism about risk, the key value judgment; this forces a choice among different pathologists' findings, and that secondary choice itself may be affected by value considerations.

In describing the basis of their ratings, the observers appeared to be using an estimate of current degree of consensus among scientists to help them judge the extent to which a particular component is "scientific." For example, rationales for rating were typically accompanied by statements like "No good scientist would question this approach," or "the best scientists don't agree on this now."

This is not the only possible definition of the concept, as outlined below.

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The key question in distinguishing scientific judgments from value judgment is the definition of the adjective "scientific." Alternative definitions have different implications.

Three distinct uses of the term "scientific" are discernable:

1. Consensus. A component is "scientific" to the extent that qualified scientists agree on the way to interpret particular data.
2. Empirical confirmation. A component is "scientific" if it is subject to confirmation or disconfirmation by the scientific method -- that is, the question can be resolved by future scientific tests or other findings.
3. Expertise. A component is "scientific" if, in practice, it must be determined by scientists because lay persons cannot be easily trained to understand all the complex factors that must be considered in making a final choice. (For example, lawyers cannot be expected to learn to read bioassay tissue slides competently and must, for this reason, defer to pathologists.)

The general question in the study performed by the Committee on the Institutional Means for Assessment of Risks to Public Health may be viewed as, "What elements in a risk assessment should be left to the scientists to decide?" The superficial answer, of course, is, "the scientific questions." The three definitions of "scientific" have different practical implications for managing risk assessments:

- Use of the consensus definition is attractive because it provides a dynamic, flexible approach to a dynamic scientific field. As scientific consensus forms a particular question, that question would move beyond the reach of nonscientific judgment. For our purpose, however, its usefulness of the consensus definition is limited by the difficulty in operationalizing it; for example (as the case of Arkansas creation science testimony demonstrates) a few eminent scientists can be found who will oppose many widely-held scientific theories--which would mean that very few components indeed would even be defined as "scientific." A criterion of unanimity is impossibly high. A lesser standard of "majority support" is impractical, too. Historians of science point out that science, by its very nature, cannot be democratized; very frequently the majority views of scientists are upset by new scientific findings that are, at first, resisted by a numerical majority of scientists. The central problem is that science has no centralized system of authority--that is, science has no formalized way to certify the dominance of particular theories for the convenience of policy formulators.

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- Use of the empirical confirmation definition is perhaps, the best literal definition of the term "scientific"--though it, too, may be difficult to operationalize. This definition directs attention to a central puzzle in the use of scientific expertise in policymaking; is it true that experts have a better "feel" for the answers to as yet untested scientific questions than laypersons? Some may doubt that scientists' informed hunches are more reliable than those of nonscientists. And even if scientists are better at guessing future scientific answers than lay persons, they may not guess in unison, leaving unsolved the familiar issue of what a policymaker should do when different scientists give different answers.
- Use of the expertise definition raises other operational questions. Does the layperson or the scientist decide whether a particular component is too complex for lay decision making? How does the lay decision-maker make sure that the expert's personal values do not affect the expert's analysis?

For risk assessment, the term "value judgment" is synonymous with "selection of the appropriate degree of conservatism."

For all the components seen as reflecting "value judgment," the underlying question appears to be how conservative a judgment to make in the face of scientific uncertainty. The choice for these components is essentially a matter of determining whether to employ principles of risk-averseness, which would lead to the use of worstcase assumptions, or whether principles of risk-tolerance should be employed.

SOME GENERAL OBSERVATIONS ON MANAGING RISK ASSESSMENTS

A review of the components of risk assessment leads to the following propositions:

A review of the components of risk assessment confirms the difficulty of managing risk assessment in the federal government.

Risk assessments are performed in many diverse programs in the federal government. Ideally, these assessments should: (a) reflect the latest scientific advances in knowledge and (b) be consistent. Federal management of assessments is greatly complicated by several facts that are inherent in risk assessment:

- There are many points in an individual assessment where discretion must be applied to cope with scientific uncertainty--and the results of an assessment are very sensitive to the assumptions inserted at all these points.

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- It is difficult to distinguish in any objective way the scientific and the extra-scientific considerations affecting the choices among these assumptions.
- Many different scientific disciplines may be germane to a particular assessment, and multiple expertise may be involved in resolving particular components of an assessment.
- The choice of assumptions cannot be determined generically--many must be left to case-by-case judgment of the facts at hand for a particular substance. Reducing risk assessment to a set of predetermined discision rules could preclude the accommodation of scientific data unique to individual cases.

If risk assessment truly is an inextricable mix of scientific judgment and value judgment, the best operating principle may be to make sure that the assumptions made in assessing risk are rountinely made explicit; in this way, they can be routinely subjected to both scientific and political scrutiny.

To summarize results from the last section, there is no practical objective definition of the term "scientific," and even if we employ subjective ratings by informed observers we find it difficult to distinguish scientific judgment from value judgment in risk assessment.

It is therefore impractical to partition the responsibilities for risk assessment between distinct groups of scientists and policy officials. This leaves no practical alternative but to subject the assessments themselves--whoever performs them--to the independent review of both scientists and responsible policy officials.

This line of argument leads to three propositions:

1. Risk assessments should routinely identify each area of inference where scientific uncertainty is confronted, and should state the analytic choice(s) made in each area.
2. Risk assessments should routinely be reviewed by some body of scientific experts, which should ascertain whether the assumptions made are consistent with current science.
3. Ultimate responsibility for all assumptions made should be borne by policy officials in order to ensure that any value judgments applied are subject to democratic processes.

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The "Parameterization Tactic" may be of little practical use.

One method that has been widely endorsed as a device that separates scientific and value judgment may be termed the "Parameterization Tactic"; it suggests that when there is scientific uncertainty in a risk assessment, the analyst should express the range of scientifically acceptable values and proceed with a multi-faceted analysis. For example, the P. Tactic holds when two or three interspecies conversion factors are possible, the calculation should be done two or three ways, and each value carried forward--presumably in tabular form--for the decision-maker to choose among on policy grounds.

The P. Tactic is useful where there are only a few sources of uncertainty in a risk assessment. This premise rarely holds. As noted above, a typical risk assessment has 20 or more components, each with an associated uncertainty factor. This implies a risk assessment presented as a 20-dimensional matrix to the decision-maker. Such a form is likely to:

- prove incomprehensible to the policymaker
- provide uselessly wide overall ranges of risk estimates

In addition, many of the components are "all or nothing" judgments (e.g., whether benign tumors should be counted) that are difficult to express numerically. The P. Tactic cannot easily apply to hazard identification, which amounts to a series of such binary determinations.

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ATTACHMENT 36 COMPONENTS OF RISK ASSESSMENT

Hazard Identification (21 components)

Inferences from Human Data (6 Components)

1) How should results from different routes of exposure be weighted? (e.g., Can conclusions about inhalation risk be drawn from data on exposure to the same chemical in drinking water or food?)
2) How should results at different tumor sites be weighted? (e.g., Should total tumors be counted or just those of the type or organ site of primary concern?)
3) How should benign tumors be weighted in comparison with malignancies?
4) Is the study scientifically adequate?* (e.g., Does it meet minimum standards of acceptability for epidemiology? Are there flaws in study design or execution that should be kept in mind in using the study findings?)
5) Which measure of association (confidence level, excess incidence level) should be used to determine whether a study is "positive"?* (e.g., What ratio of relative risk constitutes a positive finding?)
6) How should the various available study findings be weighted?* (e.g., Should positive studies outweigh negative studies?)

Inferences from Animal Bioassay Data (11 components)

7) How should results from different routes of exposure be weighted? (e.g., Should studies involving administration by gavage be counted as valid for potential air pollutants?)
8) How should data from different tumor sites be weighted?** (e.g., Should total-body tumors be counted or just those at specific organ sites?)

* A mandatory consideration if human data are present.
** A mandatory consideration if bioassay results are present.

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9) How should benign tumors be weighted in comparison to malignancies?
10) Should tumor incidence or the number of affected animals be counted?**
11) How should results of studies showing high levels of spontaneous tumors in controls be factored in?
12) How should different treatment groups be weighted in determining whether a test is "positive"? (Should only the most sensitive dose/sex/strain be considered? Should "falloff" at higher doses be discounted?)**
13) What confidence level should be applied to classify a test as positive? (e.g., Should the 95% confidence interval be used to reject the mill hypothesis of "no causal relationship between dose and effect?")**
14) Does the study meet minimum standards for acceptability in bioassays? Are there flaws in experimental design or execution that should be kept in mind?**
15) Is the pathology adequate? (e.g., Are currently acceptable definitions of lesion types employed?)**
16) Are there physiological extenuations (e.g., A chemical's unique metabolic pathway or unique pharmacokinetics, expression at a unique organ site, possibility of a toxic mechanism-of-action) that should be considered?
17) How should varying test results be weighted? (e.g., How many positive tests are required for a finding of carcinogenicity? Should negative tests be given zero weight?)**

Inferences from Other Data (3 components)

18) Is a positive test in a particular short-term screening assay indicative of carcinogenicity?
19) What confidence level should be used to reject the null hypothesis in short-term tests?

** A mandatory consideration if bioassay results are present.

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20) How much weight should be given to risk indications from structure/activity analysis?

General

21) What relative weights should be given to available human, bioassay, and other test indicators in concluding whether a chemical is a carcinogen?**

Dose Response Assessment (10 components)

Inferences from Human Data (4 components)

22) Which results from epidemiological studies should be considered? (e.g., Should the dose response curve be based only on the steepest DR curve among epidemiology studies?)
23) What mathematical model should be used to extrapolate from observed doses to policy-relevant doses?*
24) Should the dose response relationship be expressed as "best estimates" or in upper confidence limits?*
25) How should physiological extenuations be factored in the dose-response relationship?

Inferences from Bioassay Data (6 components)

26) How should varying studies be factored into the dose response estimation? (e.g., Should the dose response estimate be based solely on the most sensitive treatment group (strain/sex)?)**
27) What mathematical model should be used to extrapolate from experimental doses to human exposure levels?**
28) What factor should be employed for interspecies conversion of dose from animal to human?**
29) Should time-to-tumor effects be incorporated?
30) Should dose-response relationship be presented as "best estimates" or "upper confidence level" data points?**
31) How should physiological extenuations (metabolic saturation effects, etc.) be factored into the dose-response estimation?

* A mandatory consideration if human data are present.
** A mandatory consideration if bioassay results are present.

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Exposure Assessment

32) What points on the "gluttony scale" (e.g., 90th percentile of exposure, 4 times average intake, hypothetical "worst case" scenario) should be evaluated?***
33) To what extent should target-organ exposure substitute for exposure or intake levels?

Expression of Overall Results

34) What are the statistical uncertainties in the assessment, and how should the range of uncertainty be presented?
35) How should allowances for the most susceptible individuals (genetically predisposed, fetuses/ infants, immunologically impaired) be made?***
36) What unit of risk (deaths? life-years lost? tumor incidence?) should be used to express ultimate results?***

*** Mandatory considerations for all quantitative risk assessments.

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FEDERAL RISK ASSESSMENTS FOR POTENTIAL CARCINOGENS: AN EMPIRICAL REVIEW

Robert I. Field

Lawrence E. McCray

INTRODUCTION

There is danger that discussion of federal agency performance in assessing risks are based on anecdotal and inaccurate conceptions of actual agency practices. The evaluation of ways to improve risk assessment is necessarily based on some notion of what a "typical" agency risk assessment is like, and will not be helpful if the evaluator is misinformed about current practice.

The purpose of this paper is to summarize available empirical information on the nature of the policy problem of chemical carcinogenicity and the federal regulatory response. In general, the results are somewhat disappointing: a detailed empirical documentation of risk assessment practices in federal agencies would be a massive undertaking, which perhaps helps to explain why none has yet appeared. Some literature does exist on discrete aspects of the area, however, and a partial picture can be assembled. We have attempted to provide below what objective answers exist to basic questions concerning risk assessments. The questions include:

How big is the overall regulatory problem? One often hears the plaintive remark that "everything seems to cause cancer nowadays," but the number of chemical regulations that actually reach national headlines remains relatively small. How many suspected carcinogens are there, and what is the state of scientific knowledge about them?

Who regulates, and how much? What legislation governs the regulation of potential carcinogens, and what agencies and programs implement these laws? Has the government, as some have said, rushed to ban all suspect chemicals, or has it, has others have feared, moved only deliberately after it has assembled substantial proof of human hazard?

NOTE: This paper was originally prepared for the use of the National Research Council's Committee on the Institutional Means for Assessment of Risks to Public Health. It is not intended to present independent positions or interpretations on scientific or policy matters. It does not necessarily reflect the judgment or position of the Committee or the National Research Council. It has not been subjected to the internal review procedures that apply to reports prepared by NRC committees.

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What is a typical risk assessment like? Discussions of risk assessment often assume that federal risk assessment is a well-characterized, routinized and homogeneous process. Is the assumption accurate? If not, why not?

KNOWLEDGE ABOUT CHEMICAL CARCINOGENS AND THE FEDERAL REGULATORY RESPONSE

One American in four will contract cancer during his or her lifetime, and the weekly death toll from the disease exceeds 1000. Current scientific understanding of cancer incidence leads to a conclusion that a large faction of these cases could have been prevented if the causative agent could have been identified and public exposures reduced or eliminated. The actual proportion of preventable cancers is still being discussed, with figures as high as 90% suggested; the U.S. Government's Second Annual Report on Carcinogens more cautiously states that “many scientists now believe that about one-third to two-thirds of all cancers are agents contained in the air, water, food, or soil” (NTP, 1981).

What We Know About Chemicals and Cancer

The basic problem for public policy, of course, is that current scientific theories of cancer do not permit a definitive identification of general classes of chemicals that cause cancer, and, accordingly, this leaves a very large number of chemicals to be assessed individually. The Chemical Abstract Service of the American Chemical Society lists well over 4 million known substances, with the number increasing by an average of 6,000 each week (Maugh, 1978). As of this time, it is thought that as many as 63,000 chemicals were “in common use” (Maugh, 1978) and EPA estimated that as of 1979, 44,000 were used commercially (Roderick, 1981). About 55,000 synthetic chemicals were produced and used in significant quantities as of 1978, with 1,000 new ones being introduced each year (Ames, 1979). According to one estimate, the manufacture of synthetic organic chemicals has doubled every seven to eight years (Davis and Magee, 1979).

The number of chemicals under the jurisdiction of any single federal program may be very large. For example, EPA estimates that there may be as many as 1,500 different active ingredients in pesticides. FDA estimates that about 4,000 active ingredients are used in drugs, and about 2,000 other compounds are used for purposes such as promoting stability and restricting bacteria growth. In foods, there are thought to be 2,500 additives used for nutritional value and flavoring and 3,000 used to promote product life (Maugh, 1978). Another 12,000 chemicals are indirect food additives (Flamm, 1981).

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The evidence on carcinogenicity for any one of these chemicals is likely to be highly limited. The most direct type of evidence is that from epidemilogical studies of the effects of exposure of a chemical to humans. However, epidemiological studies of cancer are expensive, time-consuming, and fraught with difficulties--not the least of which is the problem of establishing the actual existence and level of past human exposures to any particular suspect chemical. As a result, direct human evidence is available for only a few chemicals; in fact, the International Agency for Research on Cancer lists fewer than 60 chemicals as having been adequately evaluated as cancer hazards in humans (IARC, 1980). IARC lists 32 chemicals and 4 industrial processes that have been associated with cancer through analysis of human data (Davis, 1981). At least fragmentary evidence is available on other compounds; in fact, 82 chemicals are counted as showing “some epidemiological evidence” of carcinogenicity (Maugh, 1978).

The limitations on direct human evidence necessarily throw the spotlight on animal testing. While reliance on bioassays can be used to inform policy decisions on many more chemicals, the overall supply of test data cannot be characterized as rich. It has been estimated, for example, that only about 7000 chemicals--less than 20% of the number of chemicals said to be in common commercial use--have ever been tested. Of these, only 1500 are said to have been tested under what are presently considered to be scientifically adequate conditions (Toxic Substances Strategy Committee, 1980), although one NCI official estimates that only 3500 of the 7000 are “completely inadequate” (Maugh, 1978). More striking is the fact that the volume of test results is not expanding very rapidly. It is estimated that only 100 to 300 chemicals are newly subjected to animal bioassay annually (Maugh, 1978). This number is limited somewhat by the current expense of lifetime animal exposure studies--in the range of $300,000 to $500,000. In addition, the total volume is limited by the total available supply of toxicologists, pathologists, and lab facilities, which is said to permit no more than 500 new bioassays each year (Maugh, 1978).

How many chemicals have been identified as carcinogens from the testing that has been completed? There is no simple answer to this simple question, and a review of published estimates demonstrates that estimates depend heavily on the assessor's standard of proof. It is estimated that 1500 (a little over 20%) of the 7000 chemicals tested show at least some positive results; if one-half of these are assumed to reflect adequate test methods, 750 chemicals can be counted as animal carcinogens (Maugh, 1978). This number is consistent with the Toxic Substance Strategy Committee's (1980) estimate that 600-800 compounds show “substantial positive evidence” in animal tests. IARC's estimate for the number of “suspect human carcinogens” based on animal studies is about 300; while the number of “carcinogens” is less than 200 (Tomatis, 1978). OSHA's controversial classification scheme for carcinogens reflected results from short-term tests as well as longer-term bioassays. OSHA counted 261 “proven” carcinogens, which

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it said has produced either two positive bioassays or one positive bioassay and two or more positive short-term tests. OSHA listed another 196 “suspect” chemicals, which had produced one positive bioassay or positive short-term test (Maugh, 1978).

What do we know about exposure patterns for these suspect carcinogens? Other than the obvious conclusion that, since many are produced commercially, workplace risk of exposure to many must be assumed, we found no empirical summary. NTP analyzed where exposures to 88 carcinogens substances are found (National Toxicology Program, 1981). While not a comprehensive list, the compounds studies are described as those thought to have the strongest positive results based on the findings of IARC, the NTP/NCI Carcinogenesis Bioassay Program, and various agencies. Two occur naturally (aflatoxin and cycasin), and two are sources of major exposure in food and cosmetics (saccharin and safrole). There are eight pesticides and 14 pharmaceuticals among the 88. The remaining 62 include industrial chemicals, miscellaneous chemicals and analogs, industrial processes, and industrial byproducts.

The Regulatory Response

Authority to restrict public exposures to toxic substances is distributed among 24 statutes that are administered by regulatory agencies (Toxic Substances Strategy Committee, 1980). Although the oldest of these is the Federal Food, Drug and Cosmetic Act of 1938, the laws are remarkable for their relative recency; on average, the 24 laws have been on the books for only 16 years in 1983. For potential carcinogens, the major regulatory programs are concentrated in EPA, FDA and OSHA. The sheer number of chemicals in commerce gives any one regulatory program an enormous queue of chemicals to review for regulatory action. EPA has subjected 3,500 chemicals to some sort of active review as shown in its Chemical Activities Status Report. There are so many suspects in the workplace that it has been estimated that it would take OSHA over 100 years to regulate all the known hazards on a substance-by-substance basis (Davis, 1981).

We discovered no convincing attempt to account for the federal government's cumulative disposition of the chemicals on any of the various lists of suspected carcinogens. One account (Roderick, 1981) reports that the U.S. has regulated only ten of the approximately 30 agents listed by IARC as carcinogens from evidence in epidemiological studies, and that only 8 have been regulated that appear on an IARC list of 111 chemicals for which bioassay results indicate carcino-genicity. While this record may give credence to a theory that the government moves slowly on potential carcinogens, in fact many more than 18 chemicals have been controlled, and it has proven difficult to compile definitive lists of government actions that are based on cancer hazard.

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A review of federal carcinogen regulation reported 43 substances that had been regulated as of 1978 as recognized carcinogens (Roderick, 1981). Six different statutes provide authority for these actions, and 43 rules were issued, although not in a one-to-one correspondence to the chemicals. A considerable amount of interagency overlap is evident, with asbestos being regulated under three programs, vinyl chloride under five, and DDT under two.

Another, more comprehensive study found a total of 102 substances that have either been regulated, been proposed or considered for regulation under several (but not all) statutes (OTA, 1981). A summary of the status of these chemicals, prepared in 1980, is presented as Table 1. It reveals two dominant trends in the distribution of federal efforts:

1. EPA has had the widest experience, FDA and OSHA somewhat less, and CPSC the least:

- 56 were addressed under the clean water program at EPA
- 29 were addressed under the clean air program at EPA
- 18 were addressed under the pesticides program at EPA
- 2 were addressed under the drinking water program at EPA
- 24 were addressed under the food program at FDA
- 18 were addressed by OSHA
- 5 were addressed by CPSC

2. There is a fair amount of interprogram overlap and some interagency overlap:

- there were 152 agency actions on the 102 chemicals; about 40% of all chemicals are subject of action under two or more statutes
- 39 are addressed by two or more programs
- 14 are addressed by two or more distinct agencies
- the FDA food program overlaps very little (only twice) with other federal programs
- CPSC almost always addresses substances of interest to other agencies, (four out of five instances), and OSHA often does, (11 of 18 instances).

FEDERAL RISK ASSESSMENT PRACTICES

The Art of Risk Assessment

For all of the chemicals that are subjected to regulatory review of one kind or another, some sort of risk assessment must--by definition--have taken place. In some cases this may constitute a full-blown analysis of the substance including the generation of a quantitative conclusion and a formal report, while in others it may merely involve an informal, qualitative judgment that the presence of carcinogenicity is or is not established.

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TABLE 1

Substances Regulated as Carcinogens Under Various Acts

Evaluation by NCI A	IARC H	IARC A	Chemical	Statutes: CAA	CWA §307	CWA §311	SDWA	FIFRA	OSHA	FDCA	CPSA
—	—	—	2-acetylaminofluorene (2-AAF)	—	—	—	—	—	OSHA	—	—
—	PC	S	Acrylonitrile	C	RR	L	—	V	R	—	—
—	PC	S	Aflatoxin	—	—	—	—	—	—	R	—
L	—	L	Aldrin	—	RR	L	—	V	—	—	—
—	C	S	4-aminobiphenyl	—	—	—	—	—	R	—	—
—	—	S	Arsenite	—	—	—	—	V	—	—	—
—	C	I	Arsenic	P	RR	—	R[a]	R	R	—	—
—	C	I	Arsenic compounds	—	RR	L	—	R	—	—	—
—	C	S	Asbestos	R	RR	—	—	—	R[b]	—	R
—	—	S	Benz(a)anthracene	—	RR	—	—	—	—	—	—
—	C	I	Benzene	P	RR	L	—	—	R	—	R
—	C	S	Benzidine	—	RR	L	—	—	R	—	R
—	—	S	Benzo(b)fluoranthene	—	RR	—	—	—	—	—	—
—	—	S	Benzo(a)pyrene	C	RR	—	—	—	—	—	—
—	PC	S	Beryllium	R	RR	—	—	—	—	—	—
—	PC	S	Beryllium compounds	—	RR	L	—	—	—	—	—
—	—	L	Bis,2-chloroethylether (BCEE)	—	RR	L	—	—	—	—	—
—	C	S	Bis(chloromethyl)ether (BCME)	—	RR	—	—	—	R	—	—
—	PC	S	Cadmium	C	RR	—	R[a]	R	—	—	—
—	—	S	Cadmium compounds	—	RR	L	—	R	—	—	—
—	—	S	Carbon tetrachloride	C	RR	L	—	—	—	—	—
S	—	L	Chlordane	—	RR	L	—	R	—	—	—
S	—	L	Chlorobenzilate	—	—	—	—	R	—	—	—
S	—	S	Chloroform (a trihalomethane, THM)	C	RR	L	R	—	—	—	—
—	C	S	Chloromethyl ether	—	—	—	—	—	R	—	—
—	C	S	Chromium compounds (hexavalent)	—	RR	L	—	—	—	—	—
—	C	S	Coal tar and soot	—	—	—	—	R	—	—	—
—	—	N	Coke oven emissions (polycyclic organic matter; "POM")	C	—	—	—	—	R	—	—
—	—	N	Creosote	—	—	—	—	R	—	—	—
—	—	N	Cyclamates	—	—	—	—	—	—	R	—
—	—	N	D&C Blue No. 6	—	—	—	—	—	—	R	—
—	—	N	D&C Red No. 10	—	—	—	—	—	—	R	—
—	—	N	D&C Red No. 11	—	—	—	—	—	—	R	—
—	—	N	D&C Red No. 12	—	—	—	—	—	—	R	—
—	—	N	D&C Red No. 13	—	—	—	—	—	—	R	—
—	—	N	D&C Yellow No. 1	—	—	—	—	—	—	R	—
—	—	N	D&C Yellow No. 9	—	—	—	—	—	—	R	—
—	—	N	D&C Yellow No. 10	—	—	—	—	—	—	R	—
—	I	L	DDT (dichlorodiphenyltrichloroethane)	—	RR	L	—	R	—	—	—
—	—	S	Dibenzo,h,anthracene	—	RR	—	—	—	—	—	—
S	—	S	1,2-dibromo-3-chloropropane	—	—	—	—	R[a]	R	—	—
—	—	N	1,2 dibromoethane	C	—	L	—	R	—	—	—
—	—	S	3,3'-dichlorobenzidine	—	RR	L	—	—	R	—	—
S	—	S	1,2-dichloroethane	C	RR	L	—	R	—	—	—
I	I	L	Dieldrin	—	RR	L	—	R	—	—	—
—	—	N	Diethylpyrocarbonate	—	—	—	—	—	—	R	—
—	C	S	Diethylstilbestrol (DES)	—	—	—	—	—	—	R	—
—	—	S	4-dimethylaminoazobenzene	—	—	—	—	—	R	—	—
L	—	N	2,4-dinitrotoluene	—	RR	L	—	—	—	—	—
S	—	S	1,4-dioxane	C	—	—	—	—	—	—	—
—	—	N	1,2-diphenylhydrazine	I	RR	L	—	—	—	—	—
—	—	L	Dulcin	—	—	—	—	—	—	R	—
—	I	L	Epichlorohydrin	C	—	L	—	—	—	—	—
—	—	N	Ethylene bis dithiocarbamate	—	—	—	—	R	—	—	—
—	PC	I	Ethylene oxide	C	—	—	—	R	—	—	—
—	—	N	FD&C Red No. 2	—	—	—	—	—	—	R	—
—	—	N	FD&C Violet No. 1	—	—	—	—	—	—	R	—
—	—	N	Formaldehyde	C	—	L	—	—	—	—	—
—	—	N	Graphite	—	—	—	—	—	—	R	—
(S)	—	L	Heptachlor	—	RR	L	—	R	—	—	—
—	—	S	Hexachlorobenzene	—	RR	L	—	—	—	—	—
—	—	N	Hexachlorobutadiene	—	RR	L	—	—	—	—	—

Source: Assessment of Technologies for Determining Cancer Risks from the Environment, OTA, June 1981.

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Substances Regulated as Carcinogens Under Various Acts (Continued)

Evaluation by NCI A	Evaluation by IARC H	Evaluation by IARC A	Chemical	Statutes: CAA	CWA §307	CWA §311	SDWA	FIFRA	OSHA	FDCA	CPSA
—	I	L	Hexachlorocyclohexane	—	—	L	—	—	—	—	—
—	—	N	α-hexachlorocyclohexane	—	RR	L	—	—	—	—	—
—	—	N	β-hexachlorocyclohexane	—	RR	L	—	—	—	—	—
(S)	—	N	Hexachloroethane	—	RR	L	—	—	—	—	—
—	—	S	Ideno(1,2,3-cd)pyrene	—	RR	—	—	—	—	—	—
S	—	S	Kepone (chlordecone)	—	—	L	—	V	—	—	—
—	—	L	Lindane	—	RR	L	R[a]	R	—	—	—
—	—	N	Mercaptoimidazoline	—	—	—	—	—	—	R	—
—	—	S	4,4' methylene bis (2-chloroaniline)	—	—	—	—	—	R	R	—
—	—	L	α-naphthylamine	—	—	—	—	—	R	—	—
—	C	S	2-naphthylamine	C	—	—	—	—	R	—	—
—	PC	S	Nickel	C	RR	-	—	—	—	—	—
—	PC	S	Nickel compounds	—	RR	L	—	—	—	—	—
—	—	N	Nitrosamines	—	—	—	—	—	—	R	—
—	—	L	4-nitrobiphenyl	—	—	—	—	—	R	—	—
—	—	S	N-nitrosodi-n-butylamine	—	—	L	—	—	—	—	—
—	—	S	N-nitrosodiethylamine (DENA)	—	—	L	—	—	—	—	—
—	—	S	N-nitrosodimethylamine (DMNA)	C	RR	L	—	—	R	—	—
—	—	S	N-nitrosodi-n-propylamine	—	RR	—	—	—	—	—	—
—	—	S	N-nitroso-N-ethylurea (NEU)	C	—	—	—	—	—	—	—
—	—	S	N-nitroso-N-methylurea (NMU)	C	—	—	—	—	—	—	—
—	—	N	Oil of calamus	—	—	—	—	—	—	R	—
—	—	N	P-4000	—	—	—	—	—	—	R	—
I	—	N	Pentachloronitrobenzene (PCNB)	—	—	—	—	R	—	—	—
—	I	S	Polychlorinated biphenyls (PCBs: Toxic Substances Control Act-RR)	C	RR	L	—	—	—	R	—
—	—	S	β-propiolactone	—	—	—	—	—	R	—	—
—	—	S	Safrole	—	—	—	—	V	—	R	—
—	—	N	2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, "dioxin")	C	RR	—	—	—	—	—	—
(S)	—	N	1,1,2,2-tetrachloroethane	C	RR	L	—	—	—	—	—
(S)	—	N	Tetrachloroethylene (perchloroethylene)	C	RR	L	—	—	—	—	—
—	—	S	Thiourea	—	—	—	—	—	—	R	—
S	—	S	Toxaphene	—	RR	L	R[a]	R	—	—	—
(S)	—	N	1,1,2-trichloroethane	—	RR	L	—	—	—	—	—
(S)	I	L	Trichloroethylene	C	RR	L	—	—	—	—	—
S	—	N	2,4,6-trichlorophenol	—	RR	—	—	—	—	—	—
—	—	N	Trihalomethanes (THM)	—	—	—	R	—	—	—	—
—	—	N	"Tris" (flame retardant)	—	—	—	—	—	—	—	R
—	C	S	Vinyl chloride	R	RR	—	—	—	R	—	R
—	—	N	Vinylidene chloride	C	RR	L	—	—	—	—	—
—	—	—	Radionuclides	R	—	—	—	—	—	—	—

Abbreviations

NCI: National Cancer Institute data (149)

IARC: International Agency for Research on Cancer evaluation (185, 188)
- A = animal evidence
- S = sufficient evidence for carcinogenicity (for more description see Chapter 4, Appendix A)
- (S) = Class 3 of NCI, very strong evidence in 1 species, no evidence in 2nd species
- L = limited evidence for carcinogenicity
- I = inadequate evidence for carcinogenicity
- H = human evidence
- C = identified as a carcinogen from human studies
- PC = identified as a probable carcinogen from human studies
- I = inadequate evidence to reach a conclusion about carcinogenicity from human studies
- N = not evaluated

CAA	Clean Air Act	C =	being considered for regulation
CWA 307	Clean Water Act §307	P =	regulation proposed
CWA 311	Clean Water Act §311	R =	regulated
SDWA	Safe Drinking Water Act	RR =	regulation required by Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act	L =	discharge levels restricted
OSHA	Occupational Safety and Health Act	V =	voluntarily withdrawn from market
FDCA	Food, Drug, and Cosmetic Act		
CPSA	Consumer Product Safety Act		

[a]Regulation based on non-carcinogenic toxicity (in addition to those indicated). Many other listed substances encountered in the workplace are regulated because of toxicities other than carcinogenicity)

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A brief examination of two draft documents describing risk assessment at EPA reveal on the one hand the extensiveness of the assessment, and on the other hand the infrequency with which detailed formal analyses are performed. A review of 155 chemicals under current examination by two or more EPA offices shows that all but four have undergone risk assessments. The great majority, moreover, have been assessed more than once, with 53 having been studied from two to seven times. The assessments vary from formal analyses to shorter reports by the Carcinogen Assessment Group (CAG) to brief summary risk assessments. In all, only 18 of the 155 substances were subjected for formal risk assessments, while 71 went through preliminary or summary risk assessments. A listing of the activities of CAG itself, reveals that it has prepared over 200 reports on about 110 chemicals or classes of chemicals.

A second study examined the analyses and documentation prepared by the agency in the regulation of three carcinogenic chemicals: cadmium, trichloroethylene, and arsenic. For cadmium, a total of 21 agency reports were created, of which nine dealt primarily with exposure assessments and seven with health and environmental effects. For trichloroethylene, eight reports were involved, with five dealing with exposure and one with health and environmental consequences. For arsenic, there were 16 reports, of which 12 analyzed exposure and seven health and environmental effects.

If the EPA experience is typical, federal risk assessment activity is neither uniformly rigorous or uniformly cursory. Examples of the two extremes may be seen in EPA's pre-market notification (PMN) procedures for pesticides and FDA's new drug application (NDA) process. EPA receives large numbers of notifications each year, and must make its decisions within 90 days of receipt (although this statutory deadline is not invariably met). A typical notification involves the submission of very little toxicological data, and the agency is often left to infer risk levels from a chemical's physical structure, chemical properties, and from the notifying company's estimates of future production, volume, and uses. EPA rarely demands further information. Hazard assessments are done for all substances as notifications come in, but detailed quantitative risk assessments are only performed when strong positive results are indicated. At FDA, on the other hand, large stacks of toxicological information are submitted with all NDA's. Exposures for drugs are, in comparison with PMN chemicals, easy to characterize, making risk assessments much simpler. FDA generally takes about 20 months to analyze an NDA, and in the vast majority of cases, it requests additional data from the applicant (GAO, 1980).

The Diverse Functions of Risk Assessment

Risk assessment plays different roles in the regulatory process. These roles fall into two general categories: priority setting and analysis of regulatory controls. The two roles imply distinct demands on risk assessors.

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Priority setting. Regulatory agencies typically have potential jurisdiction over a large number of substances. Circumstances force them to allocate their resources to a few at a time. Common sense and public opinion--if not their own policies--induce agencies to try to devote their attention mainly to the largest hazards. This allocation decision requires some sort of de facto risk assessment. Some notion of relative hazard--implicit or explicit, internally generated or imposed by outside groups--is necessary for this function. A part (and, for some critics, a major part) of the general criticism of federal regulation is that the agencies are not setting their priorities sensibly or systematically. In general, it appears that agency risk assessments for priority setting have been informal, and less systematic and visible, than for assessing regulatory controls.

Agencies set priorities in two areas: regulatory screening and testing. Regulatory screening involves decisionmaking about which substances should be selected--and often in what order--for serious formal regulatory review. Virtually all programs have this problem, although there is one important variation. Some programs cover a finite and known set of chemicals that must be reviewed. Here, the order of the regulatory reviews is the key question, and the job of the risk assessor may be to help the agency implement a “worst-first” or another reasoned approach. Some such thinking, for example, is relevant to OSHA's decisions about which occupational standards (cotton dust, benzene, etc.) it will review first. Similarly, EPA pesticides program has long had lists of “suspect” pesticide ingredients, and it has had to decide which ones to formally consider for cancellation or for new controls. Other programs, most prominently those that must in effect grant official licenses for the production or use of new products or substances, are forced to categorize relative risk on a case-by case basis so they can decide which new applications to concentrate on. Examples include FDA review of new food additives and applications to EPA for federal registration of new pesticides. In both variations, however, the screening function is the same: some sort of relative rating or ranking of risk must be accomplished, however imprecisely.

Variations among screening efforts--even within a single regulatory agency--are illustrated by three EPA programs. These cases dramatize the range of agency control over the quality and quantity of data available for risk assessments used in screening.

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Case 1: Premanufacturing Reviews: Screening Based on Sketchy Biological Data

EPA's Office of Toxic Substances is charged to oversee the manufacturing of new chemicals under Section 5 of the Toxic Substances Control Act. Section 5 regulations require pre-manufacturing notification (PMN) but do not require the manufacturer to perform toxicity tests. Consequently, assessors usually must screen in order to isolate the few chemicals needing detailed regulatory review from scarce data. EPA has had to rely heavily on analysis of structure activity relations (SAR) and mutagenicity data, when available, to do this screening. The agency reported it had considered drawing up risk assessment criteria for screening, but found that the limited amount and variety of information to be weighed in such decisions precluded their developing explicit criteria. Each chemical is considered on a case-by-case, necessarily judgmental basis.

Case 2: Pesticide Regulation: Qualitative Screening Based on Agency Data Requirements

EPA's Office of Pesticide Programs oversees the federal registration and reregistration of pesticides. In contrast to the PMN process, pesticide regulations require the manufacturer to perform a number of tests dealing with acute and chronic toxicity. In the screening process, each active pesticide ingredient, (and its metabolites or degradation products) is measured against a set of qualitative risk criteria, or "triggers." Specific criteria are detailed for carcinogenic, mutagenic, and teratogenic responses. If a pesticide reaches or exceeds these risk criteria, OPP shifts to a higher regulatory gear; it issues a "rebuttable presumption against regulation" and undertakes a more elaborate process to weigh benefits against risks.

Case 3: Airborne Carcinogens: Screening Based on Quantitative Data

In some cases, agencies have fairly extensive quantitative data for a list of chemicals, but limitations on agency resources preclude regulating the entire list. Setting regulatory priorities may require a chemical-by-chemical quantitative comparison of the health risk. EPA's Carcinogen Assessment Group (CAG) reports that it has performed such a qualitative analysis for the Office of Air Programs to help it determine which air pollutants should be regulated first. OSHA's 1980 Cancer Policy has suggested a similar use for quantitative risk assessment to determine which chemicals in a particular category should be regulated first.

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A second distinct type of priority setting involves the establishment of testing priorities for substances that lack adequate data to permit risk decisions. Risk assessment--formal or informal--is an inherent element in decisions about such research/testing priorities at such organizations as the National Toxicology Program, the National Center for Toxicological Research, and the research efforts of agencies themselves.

Establishing regulatory controls. The other broad category of use for risk assessment is to help determination of what appropriate policy measures, if any, are required to protect public health. This application has received the most attention in public discussions of regulation and its deficiencies, and, in general, is the use for which the most formal versions of the art are found.

Here, too, there are wide variations in what is expected of risk assessors. One source of variation is the nature of the statutory direction to the agency on how it should weigh various factors in reaching control decisions. Table 2 summarizes the ten regulatory statutes administered by the four major federal regulators: EPA, FDA, OSHA, and CPSC. There are shades of difference--sometimes in different sections of the same statute--in the degree of protection required, and, more salient, in the relative weights that agencies are instructed to place on risk, control costs, and technical feasibility. This latter factor may be divided into three approaches.

First, several laws require a balancing of costs and benefits. Such statutes generally call on the agency administering a regulatory program to weigh the benefits to be achieved through an action, including the reduction in public health risk against such costs as the economic hardship imposed on those being regulated. On some instances, Congress has explicitly listed factors to be balanced in decisions, while in others, this approach has been read into risk legislation by courts in response to vaguer mandates specifying the reduction of "unreasonable" risks. Examples of explicit balancing provisions are found in the pesticide law and the safe drinking water law, while examples of implicit balancing are found in the toxic substances law. (Details of these and other examples can be found in Table 2.) The role of risk assessments under these schemes is usually quite clear. It provides an explicit way for measuring, either quantitatively or qualitatively, the benefits that regulatory actions will provide.

Second, some laws call for mandatory control techniques whenever a hazard is affirmed. These include the outright ban of products under the Delaney clauses in the food law, and the parts of the clean air law that specify "an ample margin of safety" in emissions standards. This type of statute provides a need for the hazard identification phase of risk assessment, but since the control action is specified once the hazard is affirmed, the contribution of the dose-response information is less clear.

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TABLE 2

Public Laws Providing for the Regulation of Exposures to Carcinogens

Legislation (Agency)	Definition of toxics or hazards used for regulation of carcinogens	Degree of protection	Agents regulated as carcinogens (or proposed for regulation)	Basis of the legislation	Remarks
Federal Food, Drug and Cosmetic Act (FDA)					
Food	Carcinogenicity for additive defined by Delaney Clause	No risk permitted, ban of additive	21 food additives and colors	Risk	
	Contaminants	"necessary for the protection of public health..." sec. 406 (346)	Three substances—aflatoxin, PCBs, nitrosamines	Balancing	
Drugs	Carcinogenicity is defined as a risk	Risks and benefits of drug are balanced.	Not determined	Balancing	
Cosmetics	"substances injurious under conditions of use prescribed."	Action taken on the basis that cosmetic is adulterated.	Not determined	Risk. No health claims are allowed for "cosmetics." If claims are made, cosmetic becomes a "drug."	
Occupational Safety and Health Act (OSHA)	Not defined in Act (but OSHA Generic Cancer Policy defines carcinogens on basis of animal test results or epidemiology.)	"adequately assures to the extent feasible that no employee will suffer material impairment of health or functional capacity..." sec. 6(b) (5)	20 substances	Technology (or balancing)	
Clean Air Act (EPA)					
Sec. 112 (stationary sources)	"an air pollutant...which ...may cause, or contribute to, an increase in mortality or an increase in serious irreversible, or incapacitating reversible, illness." sec. 112(a) (1)	"an ample margin of safety to protect the public health..." sec. 112(b) (1) (B)	Asbestos, beryllium, mercury, vinyl chloride, benzene, radionuclides, and arsenic (an additional 24 substances are being considered)	Risk	Basis of the Air-borne Carcinogen Policy
Sec. 202 (vehicles)	"air pollutant from any ...new motor vehicles... or engine, which ...cause, or contribute to, air pollution which may reasonably be anticipated to endanger public health or welfare." sec. 302(h) (1)	"standards which reflect the greatest degree of emission reduction achievable through ...technology ...available..." sec. 202(b) (1)(a) (1)	Diesel particulates standard	Technology Sec. 202(b) (4) (B) includes a risk-risk test for deciding between pollutant that might result from control attempts	Sec. 202(b) (4) (A) specifies that no pollution control device, system or element shall be allowed if it presents an unreasonable risk to health, welfare or safety
Sec. 211 (fuel additives)	Same as above (211(c) (1)).	Same as above (211(c) (2) (A)).	—	Balancing Technology-based with consideration of costs but health-based in requirement that standards provide ample margin of safety	A cost-benefit comparison of competing control technologies is required
Clean Water Act (EPA) Sec. 307	Toxic pollutants listed in Committee Report 95-30 of House Committee on Public Works and Transportation. List from consent decree between EDF, NRDC, Citizens for Better Environment and EPA.	Defined by applying BAT economically achievable (Sec. 307(a) (2)), but effluent levels are to "provide(s) an ample margin of safety" (sec. 307(a) (4))	48 substances listed as carcinogens by CAG.	Technology	
Federal Insecticide, Fungicide, and Rodenticide Act and the Federal Environmental Pesticide Control Act (EPA)	One which results in "unreasonable adverse effects on the environment or will involve unreasonable hazard to the survival of a species declared endangered..."	Not specified.	14 rebuttable presumptions against registrations either initiated or completed, nine pesticides voluntarily withdrawn from market	Sec. 2(bb) Balancing "unreasonable adverse effects..."	"Unreasonable adverse effects" means unreasonable risk to man or the environment taking into account the economic, social, and environmental costs and benefits."

Source: Assessment of Technologies for Determining Cancer Risks from the Environment, OTA, June 1981.

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Public Laws Providing for the Regulation of Exposures to Carcinogens (Continued)

Legislation (Agency)	Definition of toxics or hazards used for regulation of carcinogens	Degree of protection	Agents regulated as carcinogens (or proposed for regulation)	Basis of the legislation	Remarks
Resource Conservation and Recovery Act (EPA)	One which "may cause, or significantly contribute to an increase in mortality or an increase in serious irreversible, or incapacitating reversible, illness; or, pose a. . . hazard to human health or the environment. . . ." sec. 1004(5) (A) (B)	"That necessary to protect human health and the environment. . . ." sec. 3002-04	74 substances proposed for listing as hazardous wastes	Risk. The Administrator can order monitoring and set standards for sites.	
Safe Drinking Water Act (EPA)	"contaminant(s) which . . may have an adverse effect on the health of persons." sec. 1401(1) (B)	"to the extent feasible. . . (taking costs into considerations. . . ." sec. 1412(a) (2)	Trihalomethanes, chemicals formed by reactions between chlorine used as disinfectant and organic chemicals. Two pesticides and 2 metals classified as carcinogens by CAG, but regulated because of other toxicities.	Balancing	
Toxic Substances Control Act (EPA)					
Sec. 4 (to require testing)	substances which "may present an unreasonable risk of injury to health or the environment." sec. 4(a) (1) (A) (i)	Not specified.	Six chemicals used to make plastics pliable.	Balancing: "unreasonable risk"	
Sec. 6 (to regulate)	substances which "present(s) or will present an unreasonable risk of injury to health or the environment." sec. 6(a)	"to protect adequately against such risk using the least burdensome requirement" sec. 6(a)	PCBs regulated as directed by the law.	Balancing: "unreasonable risk."	
Sec. 7 (to commence civil action against imminent hazards)	"imminently hazardous chemical substance or mixture means a. . . substance or mixture which presents an imminent and unreasonable risk of serious or widespread injury to health or the environment."	Based on degree of protection in sec. 6			
Federal Hazardous Substances Act (CPSC)	"any substance (other than a radioactive substance) which has the capacity to produce personal injury or illness . . . "15 USC sec.	"establish such reasonable variations or additional label requirements. . . necessary for the protection of public health and safety . . . "15 USC sec.		Risk	"Highly toxic" defined as capacity to cause death, thus toxicity may be limited to acute toxicity.
Consumer Product Safety Act (CPSC)	"products which present unreasonable risks of injury. . . in commerce," and " 'risk of injury' means a risk of death, personal injury or serious or frequent injury." 15 USC sec. 2051	"standard shall be reasonably necessary to prevent or reduce an unreasonable risk of injury." 15 USC sec. 2058	Five substances: asbestos, benzene, benzidine (and benzidine-based dyes and pigments), vinyl chloride, "tris"	Balancing: "unreasonable"	Standards are to be expressed, wherever feasible, as performance requirements.
	"'imminently hazardous consumer product' means consumer product which presents imminent and unreasonable risk of death, serious illness or severe personal injury." 15 USC sec. 2051				

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Similarly, some statutes call for consideration of technological or economic feasibility as the only limiting factors on the control of risks. Examples are the sections of the clean air and clean water laws that specify "best available technology" or "best practicable technology," and the hazardous substances section of the Occupational Safety and Health Act, which mandates the most stringent standards that are "feasible." In these schemes, the identification of risks is the most important phase. Dose-response information can also play a role, though, in determining the effectiveness of different control methods. Furthermore, under the occupational health law as interpreted by the Supreme Court, the agency has been encouraged to measure risks to see if their diminution through regulatory actions is in rough accord with the costs of control.

Some observers suggest that the importance of these statutory distinctions should not be exaggerated--that, as a practical matter, some sort of informal cost-benefit comparisons are necessary even if the statute seems to discourage formal quantification. The implication is that formal risk assessments could find practical use--either more or less visibly--in all programs.

There is also a practical difference between use of risk assessment in programs that involve pre-market approval of substances and in programs that operate through other post-hoc mechanisms, such as environmental emission limits. A study of federal risk assessment practices prepared by Clement Associates found that this distinction was the greatest single statutory determinant of the way in which risk assessments were conducted (Cleancut Associates, 1981). The most important effect of this difference may lie in the fact that pre-market approval programs, such as those for new human drugs and for pesticides generally empower the agency to require the submission of data to be used in a risk assessment, while other programs tend to leave agencies to fend for themselves in the acquisition of data.

Implications. These varying functions place different strains on risk assessors: the consequence may be that a single risk assessment methodology may not be able to satisfy the different functions. For example, a risk assessment done for the purpose of establishing testing priorities may, appropriately, incorporate many "worst-case" assumptions where there are data gaps, because research should sensibly be directed at those substances showing the largest and most crucial gaps. However, such simplifying assumptions may be inappropriate for risk assessments used to analyze regulatory controls, particularly where the regulator's job is partly to ensure that controls do not place wasteful strains on the economy. Similarly, for priority setting there is a premium on consistency across assessments, since the main point of the analysis is to make meaningful risk comparisons in order to direct agency resources rationally. In contrast,

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consistency may be less crucial for analyzing risk to design regulatory controls; the same general "rules of thumb" that may be reasonable for priority setting may have to yield to more sophisticated and detailed scientific arguments when a substance's commercial life is at stake, and an agency's decision will have to stand up in court. Furthermore, available resources--and the resultant analytic care--devoted to a risk assessment for deciding regulation policy for a single substance is likely to be much greater for analyzing control actions than when priorities must be set across a larger set of substances.

Procedural Factors

Federal regulatory actions can take two forms: formal and informal. These distinctions are set forth in the Administrative Procedures Act. Formal rulemaking involves an court-like adjudicatory hearing at which competing claims are heard. An administrative law judge presides, and subsequently issues a decision based on the evidence presented, both oral and written; this decision is the basis for the agency's final action. As an example, cancellation of registration for pesticides under FIFRA must follow a formal hearing. In informal rulemaking proceedings, comments from outside groups are gathered and analyzed, but an adjudicatory process is not used. The agency must respond to all substantive comments in the preamble to its final rule.

The ultimate arbiter of the adequacy of risk assessments in any proceeding is the court that scrutinizes them on judicial review. This means that one primary purpose of assessments is to satisfy judges that the agency has acted reasonably and in accordance with applicable statutory criteria. While the record from a formal adjudicatory hearing can help to convince a court that all relevant factors were thoroughly considered, either type of rulemaking action requires a carefully documented analysis, so that the actual performance of risk assessment is likely to be similar in both cases.

The influence of procedural factors on the time involved in issuing a final rule is illustrated by Table 3. All of the actions listed included hearings. The total length of the proceedings from initial action to final standard ranges up to seven years, but the average is in the range of five. It is clear that formal proceedings involve considerable commitments of time. It is likely that judges will expect thorough risk assessments as part of the support for agency actions under these circumstances. However, informal rulemaking also requires procedures that take time: Figure 1 shows the typical phases in rulemaking at EPA, which consumed about two years.

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TABLE 3 OSHA's Regulation of Chronic Hazards--Chronology (NOTE: (*) denotes carcinogens)

CHEMICAL	Initial OSHA Action	Criteria Doc./ Petition	ETS	ANPR	Proposal	Hearing	Final Standard	Judicial Review
Asbestos*	5/29/71 - Adopted existing 12 fibre standard	None	12/7/71	1/12/72	1/12/72; revised 10/9/75	3/14/72-3/17/72 (1100 page transcript)	6/7/72	4/15/74
14 Carcinogens*	5/22/72 - request for information from NIOSH	1/4/73	5/3/73; vacated 10/4/73	7/16/73	7/16/73	9/11/73-9/14/73	1/29/74	10/6/75 upheld
Vinyl Chloride*	1/30/74 - announced fact-finding hearing	1/22/74	4/5/74	None	5/10/74	6/25/74-6/28/74 and 7/8/74-7/11/74 (4000 p. transcript)	10/4/74	5/27/75 cert. den.-up-held
Noise	1974 adopted existing standard	8/14/72	None	None	10/24/74	6/23/75-7/30/75 and 9/21/76-10/8/76	pending	
Arsenic*	adopted existing standard-1971	11/8/74	None	None	1/21/75	4/8/75-4/14/75 and 9/8/76-9/14/76	5/5/78	on remand for risk assessment
Coke Oven Emissions*	9/9/71 - adopted existing standard	2/73	None	None	7/31/75	11/4/75-1/8/76 and 5/4/76-5/14/76 (5000 page transcript)	10/22/76	9/10/80 upheld
Lend*	1971 - adopted existing standard	1/73; revised 8/4/75	None	None	10/3/75	3/15/77-5/3/77; 11/1/77-11/11/77; and 12/22/77	11/14/78	pending before S. Ct.

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Beryllium*	6/27/74 adopted existing standard	1972	None	None	10/17/75	8/16/77-9/12/77	pending	
Sulfur Dioxide*	6/27/74 adopted existing standard	6/74	None	None	11/24/75	5/3/77-1		
Cotton Dust	1972 - adopted existing standard	9/26/74	None	12/27/74	12/28/76	4/5/77-4/8/77; 4/12/77; and 5/10/77-5/12/77 (105,000 page transcript)	6/23/78	6/16/81 upheld
Benzene*	Adopted existing standard - 1971	8/76	5/3/77	None	5/27/77	7/19/77-8/10/77 (3500 page transcript)	2/10/78	7/2/80 overturned
DBCP	Issuance of ETS 9/9/77	None	9/9/77	None	11/1/77	12/13/77-12/15/77	3/15/78	not appealed
Acrilonitrile*	1974 - adopted existing standard	9/29/77	1/17/78	None	1/17/78	3/21/78-4/4/78 (1300 page transcript)	10/3/78	not appealed

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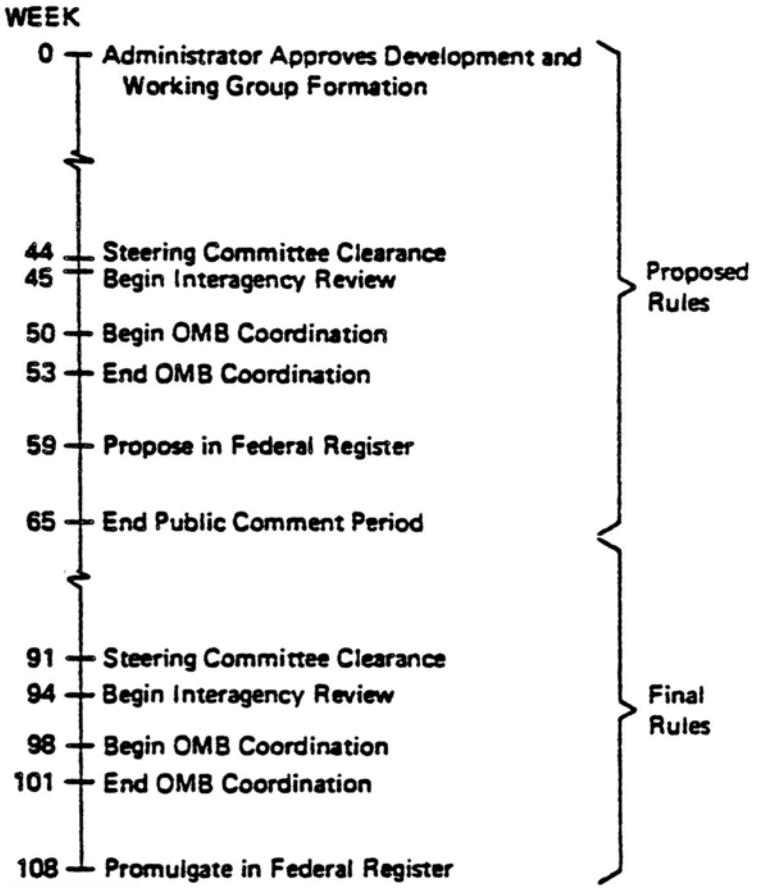
FIGURE 1



Source: Decision Making in the Environmental Protection Agency, Vol. II, NRC, 1977.

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Secular Trends

Many government regulators see risk assessment's role in regulatory decisionmaking as increasing. At OSHA, for example quantitative risk assessments had been held until two years ago to be inherently unreliable as well as unnecessary under the statutory provisions calling for the regulation of hazardous substances (Maugh, 1978). The Supreme Court's decision in the benzene case required the agency to account for the benefits of its actions, however, and OSHA responded by indicating it would include quantitative risk assessments in its regulatory process. Furthermore, NIOSH has recently begun to take more of an interest in such analyses as part of its research efforts.

Another example is FDA's Bureau of Foods, where risk assessment has gained importance as the policy of banning substances in response to any evidence of a carcinogenic risk has lost factor. Quantitative risk assessment is increasingly being used as a means of deciding where the most substantial hazards lie. A final example is the control of toxic substances at EPA, where an increasing number of statutory mandates enacted over the past decade have explicitly called for a balancing of risks and benefits in a way that previous enactments have not. Among these are FIFRA, passed in 1972, and TSCA, passed in 1976.

In addition to these specific agency examples is the direction of federal regulatory policy in general. Under Executive Order 12291, regulatory agencies are required to establish that significant actions will involve benefits to society that outweigh their costs. This will encourage the use of quantitative risk assessments, so that benefits can be measured.

Several factors have emerged over the past decade that should promote risk assessment, particularly quantitative assessment. Their influence can be particularly seen clearly in Congress's choice to include balancing criteria in more recent risk legislation (Field, 1981).

The first factor is the effect of changing economic conditions. As the financial capabilities of American industry to play a large role in eliminating risks have become more strained, pressures for a precise accounting of risks and benefits have grown. Second, changes may have occurred over time in the incremental benefits that new risk regulations can achieve. Initial interventions have in many cases produced substantial results, so that further efforts may be leading to a point of diminishing returns. Third, there has been a large expansion in recent years in the amount of data available on specific hazards, making the presence of risks easier to detect. Test have revealed a greatly increasing number of substances that are dangerous. As a result, the development of schemes for setting priorities in risk control and for comparing risks to benefits has become more highly valued. Finally, there have been advances in the methodology of risk assessment, and the public and the scientific community seem to have fewer reservations about its use.

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Consistency in Federal Risk Assessments

One of the main public concerns about risk assessment is that it is not performed consistently over time or across agencies. As outlined, there certainly are substantial variations in the size, coverage and form of risk assessment. Whether the assessments vary substantively--that is, whether the use of inconsistent approaches leads to different conclusions from the same scientific data--is less clear.

We found only one systematic attempt to address this question, and while there are interagency guidelines for cancer risk assessment, in practice it is difficult to establish whether they are followed. Those who have looked at specific assessments report that it is often difficult to trace the assumptions that were used in the analysis--so the necessary first step in establishing the degree of consistency across assessments is usually lacking. A report on risk assessment as practiced by EPA and other agencies (Clement Associates, 1981), presents several conclusions on consistency in the techniques used. Hazard assessments for carcinogens are fairly uniform as compared to such analyses for other health effects.

However, many differences in procedural details exist, the most important ones being in the choice of animal data as the basis for extrapolation, the use of correction factors for partial lifetime dosage, and the use of animal-to-human scaling factors. These variations can, in some instances, lead to differences in estimates of human risk of ten times or more. There is variability in the ways that the results of risk assessments are presented by different offices.

The Clement Report reached a number of conclusions on other agencies, including FDA, CPSC, and OSHA. The same sort of differences that were found to exist among EPA's various offices were also noted among these agencies. The major aspects of quantitative risk assessment are fairly well standardized, but numerous differences do exist. The IRLG guidelines are reported to be given uneven use, and noncarcinogenic risks tend to be more variable in their assessments than carcinogenic ones. Aside from these guidelines, there is no major mechanism to ensure consistency among the agencies.

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