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Significant Risk Decisions in Federal Regulatory Agencies

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The completion of a risk assessment does not reveal whether the assessed risk is of significant public health importance. Little attention has been paid to the development of rigorous analytic approaches to the determination of risk significance. This paper reviews a number of major FDA, EPA, and OSHA decisions regarding significant carcinogenic risks and identifies several problems that need to be explored more fully to ensure that both the qualitative and quantitative features of a risk assessment are considered in the determination of risk significance. © 1987 Academic Press, Inc.

Risk assessment is now the basis for most important regulations concerning potentially hazardous substances. Although the uncertainties in risk assessment are large, and vast improvements are needed, there appears to be no useful alternative to its use. Even considering the uncertainties, risk assessment is the most powerful device available to organize and express what can be stated about risks that are not subject to direct observation and measurement, but which nevertheless may be of concern.

Risk management is the term applied to the process of deciding whether a risk requires reduction, identifying the options for risk reduction, selecting the means for and objectives of risk reduction, and implementing those means. Risk management incorporates not only risk information, but also information on technical feasibility, cost, and other social benefits, as well as political factors. The extent to which this additional information influences risk management decisions largely depends upon the requirements of applicable statutes and the habits of thinking that have evolved within the responsible regulatory agencies (NRC, 1983).

Although there have been numerous studies of and commentaries on most elements of the risk assessment–risk management process, at least one element appears to have escaped detailed analysis: the determination of whether a given predicted risk poses a significant threat to the public health and of the extent to which risk reduction is needed to achieve public health protection. Because determinations that a risk is "significant" or "insignificant" trigger or halt regulatory action, it would seem important to consider more thoroughly their bases. In this paper we first summarize actions of three major regulatory agencies—FDA, EPA, and OSHA—to regulate exposures to carcinogens. Our summary is not exhaustive and tends to emphasize actions in

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which the agencies have explicitly discussed the matter of significant risk. We describe what the agencies have themselves concluded regarding the magnitude of risk that should be considered a significant public health concern. We then attempt to draw some generalizations from these agency determinations. Finally, we identify several issues relating to these determinations that appear not yet to have been fully explored by the agencies or by observers of the regulatory process.

The risks discussed in this paper are those associated with carcinogens. Up to the present no attempts have been made to present explicit risk information for other types of toxic agents, although an analysis of the types of safety factors used to derive acceptable intake levels for non-cancer endpoints would seem also to be in order. We emphasize at the outset that the carcinogenic risks we describe are *predicted* risks, based on a variety of as yet untested assumptions about interspecies and high-to-low dose extrapolation and should not be confused with risks based on actuarial analyses. We also note that although the risks we mention are predicted, the risk assessment methodologies used by the three agencies are nearly equivalent (though not identical), so that a given risk predicted by EPA has roughly the same meaning and uncertainty as that predicted by OSHA and FDA.

A. FOOD AND DRUG ADMINISTRATION

Risk assessment has been used by the Food and Drug Administration (FDA) primarily as a basis for regulating substances added to or contaminating food, although recently FDA has extended this practice to other classes of products. Indeed the FDA was the first government agency formally to incorporate risk assessment into regulatory decision-making. In 1973 FDA proposed to define the maximally acceptable concentration of food residues of carcinogenic drugs used in food-producing animals as that which would produce a lifetime carcinogenic risk no greater than one in 100 million (10^{-8}). The FDA proposed a risk assessment methodology published in 1961 by Mantel and Bryan (Mantel and Bryan, 1961) simply because it was the only methodology then available in the scientific literature. FDA even proposed adopting the lifetime risk level (10^{-8}) suggested by Mantel and Bryan to be clearly negligible (these authors referred to the dose corresponding to a 10^{-8} lifetime risk level as a "virtually safe dose"). In effect, FDA was saying that food residues of carcinogens in this particular class of regulated agents could be present below the maximally acceptable concentration without jeopardizing the public health (FDA, 1973). Although in response to public comments FDA later changed the maximally acceptable lifetime risk to one in one million (10^{-6}) and modified the risk assessment methodology (to the linear-proportional form currently in use), risk assessment became firmly lodged as a regulatory tool (FDA, 1979a).

FDA has adopted this same approach for other classes of regulated substances that are carcinogenic. FDA permanently listed D&C Green No. 5, which contains the carcinogenic contaminant *p*-toluidine, after determining that the upper limit on lifetime risk was less than one in 30 million (FDA, 1982). The FDA also approved the color additive lead acetate, which the agency had suggested was an animal carcinogen, at a lifetime risk between one in 5 million and one in 18.5 million (FDA, 1980). In neither of these decisions did the agency state that a lifetime risk of 10^{-6} was its significant risk criterion; it simply proposed that these estimated risks were insignificant from a public health standpoint.

Most recently, the agency has extended the approach to cover directly added food ingredients, in apparent defiance of the "zero-risk" requirements of the Delaney Clause (FDA, 1985). In all these cases FDA has insisted its goal has been to satisfy the statutory requirement that color additives and substances added to food must be "safe," which, in the context of food law, has generally been defined as "reasonable certainty of no harm." FDA has further insisted that the benefits of food and color additives cannot be considered in its regulatory decisions—an additive can be introduced into food only if it has been shown to be safe. A position has thus evolved within FDA that a carcinogen can be considered safe as long as exposure to it is restricted to levels posing insignificant risks.

Predicted lifetime cancer risks less than 10^{-6} have been defined by the agency as *insignificant* in several of these decisions. In a 1979 reproposal of the animal drug residue regulation FDA stated that "a risk level of one in one million over a lifetime imposes no additional risk of cancer to the public" (FDA, 1979a). FDA has also stated that a level of a substance that presents no more than a one in one million lifetime risk of cancer "can properly be considered of insignificant public health concern" and is "the level that represents no significant carcinogenic burden in the total diet of man" (FDA, 1977).

FDA considers lifetime risks less than one in one million of no public health concern even for substances that are directly added to food and therefore clearly subject to the Delaney Clause. The most explicit statement of this policy appears in the *Federal Register* of December 18, 1985, in which FDA proposed not to act against the use of methylene chloride to extract caffeine from coffee. In the quotation presented below, the agency equates its so-called *de minimis* risk decision under the Delaney Clause with its earlier safety decisions on color additives and indirectly introduced carcinogens:

> In several proceedings involving the agency's policy for carcinogenic impurities in food and color additives, FDA has used the risk of 1 in 1 million as a standard for determining whether the calculated upper bound risk of cancer posed by an impurity is low enough to be considered "safe" within the meaning of the general safety clause.
>
> FDA believes that these uses of the 1 in 1 million risk level are indistinguishable from the use of 1 in 1 million as a *de minimis* level of risk with respect to the Delaney Clause. A finding that a substance with a 1 in 1 million risk is "safe," or that it "imposes no additional risk of cancer to the public," is the same as a finding that the risk is of no public health consequence or that it is insignificant. It is in just those circumstances, where there is no meaningful increase in public health protection from applying the strict terms of a legal standard, that the courts have found the *de minimis* doctrine to be applicable. For example, the court in *Monsanto* equated *"de minimis"* with a finding that migration of an indirect food additive is "insignificant" in a context where the court clearly recognized that the real question was the toxicity of a particular level of migration.
>
> For these reasons, FDA concludes that a risk level on the order of 1 in 1 million for cancer constitutes a *de minimis* level of risk, and that its use of that level of risk in other regulatory contexts is consistent with that conclusion. (FDA, 1985)

In the same proposal FDA described methylene chloride lifetime cancer risks to consumers (10^{-4} to 10^{-2}) and hair care specialists (10^{-3} to 10^{-2}) resulting from the use of the solvent in aerosol cosmetic products. The agency considered these risks significant and proposed to prohibit the use of methylene chloride in all cosmetic products.

Although the methylene chloride proposal and several similar proposals concerning color additives are not final agency actions, and will be subjected to judicial re-

view, they make clear the FDA's current position that the Delaney Clause was not intended to deal with insignificant carcinogenic risks.

Finally, it should be recognized that FDA has found lifetime cancer risks greater than 10^{-6} for certain classes of inadvertent food contaminants—PCBs, polychlorinated dioxins, and aflatoxins—to be acceptable, given the technical and cost limitations on reducing such risks. In the case of PCBs in fish, FDA noted, for example, that a lifetime risk of one in 14,000 (corresponding to PCB intake at a 2 ppm tolerance level) will "protect the public health adequately" (FDA, 1979b). FDA has not, however, labeled any risks greater than 10^{-6} as insignificant.

B. ENVIRONMENTAL PROTECTION AGENCY

1. Pesticides

The Environmental Protection Agency (EPA) has, in recent years, accepted food residue levels of carcinogenic pesticides posing lifetime risks as high as 10^{-6}. Agency decisions on dicamba (EPA, 1984a), cyromazine (EPA, 1984b), and thiodicarb (EPA, 1985a) were based on the same position taken by FDA on the safety of food residues of carcinogens. The Office of Pesticide Program has also used the same lifetime risk level to set tolerances for certain *N*-nitrosamine contaminants of pesticides (EPA, 1982c).

For carcinogenic pesticides that are subject to the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), EPA is required to perform a risk–benefit analysis. It appears that in most cases EPA has used the 10^{-6} lifetime risk as a rough guide to significant risk decisions, but the agency has allowed risks greater than 10^{-6} when benefits were large and has acted against pesticides posing risks less than 10^{-6} when benefits were seen as negligible. It is not clear what the upper limit in risk acceptance is for pesticides regulated under FIFRA, but there are several decisions in which EPA has accepted lifetime risks as high as ca. 10^{-4}. Several examples of EPA significant risk decisions on pesticides are presented in Tables 1 and 2. It should be noted that EPA usually considers qualitative evidence—particularly the quality and strength of the animal bioassay data—along with the quantitative risk estimates in its discussions of risk significance. Also, many of the actions against pesticides involved risks of toxicity other than carcinogenicity.

2. Carcinogenic Air Pollutants

Of relevance in determining what constitutes significant public risk is the EPA's treatment of nonoccupational risks in its regulatory decisions under Section 112 of the Clean Air Act, which provides for promulgation of National Emissions Standards for Hazardous Air Pollutants (NESHAPs). EPA has agreed with the Supreme Court's view, expressed in the *Benzene* decision (see below) that "safe" is not equivalent to "risk-free" and determined that "standards under Section 112 should protect against *significant* public health risks" EPA, 1984d).

EPA explained in its notice withdrawing proposed regulations of radionuclides from elemental phosphorus plants and other sources that two measures of risk provide important information about significance (EPA, 1984e). The first, "nearby indi-

TABLE 1

RISKS ASSOCIATED WITH EPA DECISIONS TO SUSPEND OR CANCEL PESTICIDE REGISTRATIONS: RISKS OUTWEIGHED BENEFITS

Pesticide	Exposure	Approximate lifetime cancer risk
DBCP (dibromochloropropane)[a,b]	Diet	1×10^{-7}
	Drinking water	2×10^{-6}
	Applicators	2×10^{-5}
EDB (ethylene dibromide)[a,c]	Diet (grain products)	1×10^{-4}
	Ground water	3×10^{-5}
	Applicators	4×10^{-4} to 2×10^{-1}
Pentachlorophenol (hexachlorodibenzo-*p*-dioxin contaminant)[d]	Applicators	6.4×10^{-4} to 1.5×10^{-2}

[a] EPA concluded that toxic effects other than carcinogenicity were also significant. The strength of evidence of carcinogenicity was also considered (qualitatively).
[b] EPA, 1979.
[c] EPA, 1983.
[d] EPA, 1984c. EPA proposed manufacturers reduce contaminant level so that all applicator risks were below ca. 4×10^{-4}.

vidual risk," refers to the "estimated increased lifetime risk from a source that is faced by individuals who spend their entire life (*sic*) at the point where predicted concentrations of the pollutant are highest." The second, "total population impact," refers to the aggregate risk to all exposed persons in terms of total yearly fatalities.

TABLE 2

RISKS ASSOCIATED WITH EPA DECISIONS *NOT* TO CANCEL PESTICIDE REGISTRATIONS: BENEFITS OUTWEIGH RISKS[a]

Pesticide	Exposure	Approximate lifetime cancer risks
Benomyl[b]	Diet	7×10^{-6} to 7×10^{-5}
	Workers/users	7×10^{-7} to 5×10^{-6}
Thiophanate-methyl[b]	Diet	7×10^{-6} to 7×10^{-5}
	Workers/users	7×10^{-7} to 5×10^{-6}
Ethylene bisdithiocarbamates[c]	Diet	5×10^{-5} to 5×10^{-4}
	Applicators	9×10^{-5} to 1×10^{-2}
Trifluralin (including restrictions on *N*-nitrosamine contaminant)[d]	Diet	5×10^{-7}
	Applicators	1×10^{-7}

[a] EPA is currently reassessing the first three decisions listed.
[b] EPA, 1982a.
[c] EPA, 1982b. Animal oncogenicity studies on the pesticides and their common metabolite, ethylenethiourea, were considered flawed. EPA required restrictions to reduce applicator exposure and also imposed additional testing requirements.
[d] EPA, 1982c.

TABLE 3

EPA NESHAPs INSIGNIFICANT RISK DECISIONS[a,b]

Substance and source	Maximum individual risk	Aggregate risk (extra cancers/year)
Radionuclides Elemental phosphorus plants	1.0×10^{-3}	0.06
Radionuclides DOE facilities	1.0×10^{-4} to 8.0×10^{-4}	0.08
Radionuclides NRC licensed facilities	2.0×10^{-4}	0.02
Benzene Maleic anhydride process vents	7.6×10^{-5}	0.029
Benzene Ethyl/benzene styrene plants	1.4×10^{-4}	0.0057
Benzene Storage vessels	3.6×10^{-5}	0.043

[a] EPA, 1984d.
[b] EPA, 1984e.

These two estimates—individual risk and population impact—together provide a superior description of a risk than either alone, EPA has explained, because "nearby individual risk" tells us the highest risk to which anyone is subject, but not how many persons face this risk. (In fact, the number generally is small, for "generally few people reside at the points of maximum concentrations and spend their whole lives at such locations.") Conversely, "total population impact describes the overall health impact" of a substance "on the entire exposed population," but says nothing about the most exposed individuals (EPA, 1984e).

EPA has found the maximum individual risks and total population risks from a number of radionuclide and benzene sources too low to be deemed significant. For instance, benzene emissions from maleic anhydride process vents created maximum individual risks of 7.6×10^{-5} and an aggregate public health impact of ca. 0.03 extra cancer cases (EPA, 1984d). Radionuclides from Department of Energy (DOE) facilities expose a person who accrued lifetime exposure to a plant's most concentrated emissions to a risk of 1×10^{-4} to 8×10^{-4}, while, in the aggregate, only 0.08 extra cancer cases would be predicted to occur yearly, or roughly one case every 13 years (EPA, 1984e). A summary of the radionuclide and benzene risks found insignificant by EPA is provided in Table 3.

As Table 3 reveals, EPA found risks to be insignificant when the most exposed individual faced a risk in the range of 10^{-4} to 10^{-3} after 70 years of exposure to radionuclides or benzene. Of course, account must be taken of the fact that *average* personal risk would be below the maximm risk. In view of the maximum risks found insignificant by EPA, 10^{-5} seems to be in the range of what EPA might consider to be an insignificant average lifetime risk. This may be true at least in cases where, as with the sources outlined in Table 3, aggregate population impact does not exceed a fraction of a cancer yearly.

3. *Drinking Water*

In a recent interpretation of the Safe Drinking Water Act, EPA has proposed that, for "non-threshold toxicants" contaminating drinking water, such as carcinogens, no safe level of exposure can be established. The agency proposed zero exposure as the goal (Recommended Maximum Contaminant Levels) for such contaminants and then proposed Maximum Contaminant Levels (MCLs) based on considerations of technical feasibility. Under this approach, it can be presumed MCLs would have to be reduced whenever it became technically feasible to do so. This approach explicitly rejects the use of risk assessment and any notion of a finite risk that can be considered insignificant (EPA, 1985b).

4. *Superfund Cleanup*

Although no clear pattern has yet emerged, EPA appears generally to seek cleanup levels for carcinogenic contaminants of Superfund sites that ensure lifetime risks $<10^{-6}$. In the agency's official Superfund guidance documents, risk goals are stated to fall in the range of 10^{-4} to 10^{-7}, but so far emphasis has been placed on the 10^{-6} figure (EPA, 1986a).

Most of the information about risks predicted at Superfund sites appears in the so-called Remedial Investigation–Feasibility Study (RI-FS) technical documents prepared after site investigations. Based on these documents, EPA prepares decision documents (Records-of-Decision) in which the choice of cleanup plans is described. We have recently reviewed 140 Records-of-Decision on Superfund remedial actions issued from 1982 to 1985. We found risk assessment information described in only a small fraction of these documents (less than 10%). It is thus difficult to determine the extent to which risk information plays a role in the selection of remediation options and particularly whether the costs of cleanup are commensurate with the magnitude of risk reduction achieved (i.e., whether remediation is cost-effective). This conclusion is, however, limited by the fact that Records-of-Decision issued in the past year have not been reviewed to determine if the early trends have changed and because we have not reviewed the underlying RI-FS documents.

C. OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION

1. *Occupational Risks*

The Occupational Safety and Health Administration (OSHA) is the primary agency charged with assuring worker health and safety. OSHA is required to find risks significant before it may seek to regulate them. As the Supreme Court ruled in *Industrial Union Department, AFL-CIO v. American Petroleum Institute* (the *Benzene* case), the Secretary of Labor, before promulgating any safety or health standard, must "make a finding that the workplaces in question are not safe." However,

> "safe" is not the equivalent of "risk-free." There are many activities that we engage in every day—such as driving a car or even breathing city air—that entail some risk of accident or material health impairment; nevertheless, few people would consider these activities "unsafe."

TABLE 4

LIFETIME RISKS[a] OF WORK-RELATED DEATH PER 1000 PERSONS IN SELECTED INDUSTRIES, ASSUMES 45-YEAR WORKING LIFETIME[a] AND DEATH RATES REPORTED BY BUREAU OF LABOR STATISTICS FOR 1984. (USE OF DATA FOR OTHER YEARS WILL YIELD SLIGHTLY DIFFERENT ESTIMATES[b])

Industry	Lifetime deaths/1000
Mining	18.6
Construction	10.3
Transportation and public utilities	7.6
Agriculture	7.3
Manufacturing	2.0
Wholesale and retail trade	1.4
Services	1.8
Finance, insurance, and real estate	0.9

[a] BLS figures were converted to lifetime risks to permit comparison to OSHA's estimates of risks associated with occupational carcinogens.
[b] Cotter, 1986.

> Similarly, a workplace can hardly be considered "unsafe" unless it threatens the workers with a significant risk of harm. (*Industrial Union Dept.*, 1980a)

As the Supreme Court noted, individuals face a multiplicity of risks in activities they do not consider unsafe. In determining the level of occupational risk that constitutes a significant risk, an approach suggested by the Court—comparison of the risk in question to other common occupational risk levels—has been used by OSHA. The Court also suggested a lifetime occupational cancer risk of 1 in 1000 as a "rule of thumb" for identifying significant risk:

> Some risks are plainly acceptable and others are plainly unacceptable. If, for example, the odds are one in a billion that a person will die from cancer by taking a drink of chlorinated water, the risk clearly could not be considered significant. On the other hand, if the odds are one in a thousand that regular inhalation of gasoline vapors that are 2% benzene will be fatal, a reasonable person might well consider the risk significant and take appropriate steps to decrease or eliminate it. (*Industrial Union Dept.*, 1980b)

A 1 in 1000 risk level is low compared to other fatality hazards in jobs commonly thought of as "safe." On the basis of data collected by the Bureau of Labor Statistics for 1984, the average lifetime risk of a work-related death in private sector establishments with 11 or more employees is 2.9 per 1000 (assuming 45 years of employment). For persons working for 45 years in the mining, construction, and transportation and public utilities industries, the lifetime occupational fatality rates are 18.6, 10.3, and 7.6 per 1000, respectively, while those employed in the wholesale and retail trades have a risk of 1.4 per 1000 and those employed in finance, insurance, and real estate have a lifetime risk of fatality of just under 1 in 1000 (Cotter, 1986). Table 4 presents lifetime risks of work-related fatalities for a number of industries. It should be remembered that these are directly measured, not predicted risks. Note also that the figures assume little variation in the risks from year to year.

OSHA and other federal regulatory agencies have used fatality rates such as those depicted in Table 4 as "benchmarks" for evaluating the significance of worker health risks. EPA and the Nuclear Regulatory Commission (NRC), for example, have pro-

TABLE 5

ESTIMATED LIFETIME RISKS OF DEATH FROM CANCER PER 1000 PERSONS ASSOCIATED WITH OCCUPATIONAL EXPOSURE AT PREVIOUS AND REVISED OSHA PERMISSIBLE EXPOSURE LIMITS (PELs) FOR SELECTED SUBSTANCES

Substance	Cases/1000 at previous PEL	Cases/1000 at revised PEL
Inorganic arsenic[a]	148 to 767	8
Ethylene oxide[b]	63 to 109	1 to 2
Ethylene dibromide[c] (proposal)	70 to 110	0.2 to 6
Benzene (proposal)[d]	44 to 152	5 to 16
Acrylonitrile[e]	390	39
Dibromochloropropane (DBCP)[f]	—	2
Asbestos[g]	64	6.7

[a] OSHA, 1983a.
[b] OSHA, 1984.
[c] OSHA, 1983b.
[d] OSHA, 1985.
[e] Albert, 1983. Risks at previous PEL derived by linear extrapolation from current PEL risks.
[f] Risk estimated by present authors.
[g] OSHA, 1986.

posed to set federal radiation standards using as a yardstick the fatality rates prevalent in industries commonly considered to be relatively safe.

In its radiation protection proposal, EPA noted that "the risk of job-related accidental death in the safest of all major occupational categories, retail trades, [was] an annual death rate [of] 60 per million workers in 1975." This risk equates to a 45-year worklife risk of 2.7 in 1000. The Agency based its proposed radiation protection guidelines on its finding that radiation risks of a magnitude similar to 3 in 1000 "do not appear unreasonably high" because "[t]hey are comparable to risks of accidental death in the least hazardous occupations" (EPA, 1981).

In a similar vein, NRC's recent radiation protection proposal follows the approach recommended by the International Commission on Radiological Protection (ICRP), which developed its guidelines by "comparing [radiation] risk with that of workers in industries . . . which are recognized as having high standards of safety." As NRC pointed out, in such " '[s]afe' industries . . . average annual mortality due to occupational hazards does no exceed 10^{-4} [i.e., 1 in 10,000]." This annual rate amounts to a 45-year lifetime risk in excess of 4 in 1000. Like EPA, NRC proposed standards on the basis that occupational mortality risks due to radiation are "acceptable" if kept at or below this "safe industry" risk level (NRC, 1986).

Health standards promulgated by OSHA generally have stopped short of regulating occupational cancer risks below 1 in 1000, largely because of feasibility limitations. As Table 5 shows, the residual lifetime risks (i.e., those remaining after implementation of the OSHA's revised Permissible Exposure Limit) associated with the inorganic arsenic and ethylene oxide standard are in OSHA's estimation 8 per 1000 and 1 to 2 per 1000, respectively. Further, the residual risks associated with the proposed benzene standard are, according to OSHA, 5 to 16 per 1000. Note that OSHA has not made any statement about what it considers an "insignificant" occupational risk.

D. SUMMARY OF AGENCY SIGNIFICANT RISK DECISIONS

Although our review of significant risk decisions is not exhaustive, several trends emerge. With one important exception, two federal regulatory agencies (EPA and FDA) now appear to recognize the notion of "insignificant" or *de minimis* risk. At least in the past 5 years there appears to be no case in which predicted lifetime cancer risks $<10^{-6}$ have been subjected to regulation, with the possible exception of some pesticides judged to provide insignificant benefits. Although agencies and offices within those agencies have described the concept of *de minimis* risk in different ways and with varying degrees of explicitness, there appears to be almost universal acceptance of the concept.

The exception to this trend is, of course, the EPA's Drinking Water Office, which rejects, as unsafe, at least in principle, any finite risk of carcinogenesis, no matter how small.[1] The Office does, however, accept finite exposures to carcinogens, but because of technical limitations.

Decisions on cleanup goals at most Superfund sites appear to be based in part on risk analysis, but the magnitude of risk reduction achieved at Superfund sites as a function of cost is not readily identifiable from agency decision documents.

OSHA has not judged any occupational carcinogenic risk to be clearly insignificant, but has not sought to force predicted lifetime risks below ca. 10^{-3}. It appears that, at least in principle, OSHA is prepared to find some level of occupational risk insignificant.

The other emergent trend is that the regulatory agencies have found lifetime risks to the general population greater than 10^{-6}, sometimes up to $>10^{-4}$, as acceptable, either because of cost or feasibility constraints or because the size of the exposed population was small. Even the Office of Drinking Water accepts risks in this range for the trihalomethane contaminants produced as a byproduct of chlorination (EPA, 1986b). Except for decisions made by EPA's Air Office, as described above, we can find no evidence that agencies regard general population risks greater than 10^{-6} as clearly insignificant; rather, risks greater than 10^{-6} are often described as "acceptable" because reductions to the clearly negligible range are either technically infeasible or too costly.

E. PROBLEMS

Our review of agency carcinogen risk decisions and the underlying documentation suggests several types of problems that seem to us to deserve more attention.

1. Definitions of Significant and Insignificant Risks

Although there appears to be wide acceptance of the notion of significant and insignificant risks (which sometimes go by other names) and even some apparent consen-

[1] We do not sense that the Safe Drinking Water Act requires a stricter definition of safety than any other environmental statute, especially the food additive laws; but we do not pose as legal analysts.

sus on the level of risk that can be considered insignificant, there have yet to emerge clear definitions of the terms or a consistent, rigorous analytic approach to their identification in specific instances. In many cases, some type of comparison is made to show that a risk is small or large compared to other common risks, but most such comparisons appear superficial, and no clear notion of what is meant by "large" or "small" has emerged. In other cases, risks have been called significant or insignificant if the absolute number of extra cancer cases predicted is small; again, no clear notion of "large" or "small" has emerged. We also recall that the Office of Drinking Water has suggested that no finite cancer risk is small enough to protect public health; in this they appear to deviate from all other agencies and offices.

We suggest the need for clearer definitions in these areas and describe below some of the additional problems that need to be explored before such definitions can be achieved.

2. *Treatment of Uncertainties in Risk Assessment*

In most circumstances scant attention is given the uncertainties in risk assessments when significant risk decisions are made. Although many of the uncertainties are generic to all carcinogen risk assessments, many are also chemical specific. In most cases agencies simply note that the predicted risks are likely upper limits and that the actual risks may be lower. It is not obvious how uncertainties should be treated in significant risk decision-making, but it seems clear they should.

A possible reason for the lack of treatment of uncertainty is the frequent failure of risk assessors to provide to decision-makers adequate information about both the quantifiable and nonquantifiable uncertainties in these assessments.

One consequence of taking into account agent-specific uncertainties will be that determinations of significant risk will also have to be agent-specific.

3. *Risk Comparisons*

It is far from clear how to choose the appropriate background of risk against which to make comparisons. Most analysts, for example, would not compare voluntarily assumed risks to involuntarily assumed risks. But it is far from apparent how these two types of risks are to be rigorously identified. Even more difficult is the issue of the relative degrees of reliability in the risk figures being compared. Is it, for example, appropriate to compare actuarial risks to those that are merely predicted? These and other difficulties suggest to us that further attention needs to be devoted to the appropriateness of various risk comparison procedures.

One aspect of the risk comparison issue that is beginning to loom large concerns the natural background of risks in food. Food is an enormously complex collection of chemical compounds and it is almost certain that if we were to isolate individual constituents of food and subject them to standard carcinogen bioassays, a sizable fraction would be found positive. It is not overly conjectural to posit that application of our standard methods of risk assessment to these natural carcinogens would reveal food to carry a very large risk. This would mean either that our risk assessment methods are incorrect or that the natural diet contributes significantly to the overall cancer burden; both conclusions are probably correct to a degree (Rodricks and Pohland,

1982). This is a major aspect of the background risk issue that has yet to be faced by the regulatory agencies. It seems inevitable that they will have to face it.

4. *Individual vs Population Risks*

No clear trend has yet emerged on the question of whether risks to individuals, risks to populations, or both, are to be considered in significant risk decisions. Is a large risk to a small number of people more important from a public health perspective than a small risk to a large number of people? There seems no obvious way to examine this question, but it surely requires study.

These various problems are no doubt difficult and some may seem imponderable. But a rigorous approach to the significant risk question would seem to require that they be more fully explored than they have been thus far. We do not suggest that agencies reject the precedents for significant risk decision-making that have developed, but only that they consider more fully their bases in the future.

We recognize that no significant risk decision is made in a vacuum and that many factors other than risk come into play. We nevertheless hold that the first step following any risk assessment is a determination of whether the risk is large enough to threaten the public health to a significant degree. Only after such a determination is made is it necessary to consider the options for risk reduction. There is no apparent reason why all the regulatory agencies could not agree on a common analytical methodology for analyzing the public health significance of a given risk—the factors that need to be considered and the appropriate means for considering them. There is also no apparent reason why the agencies could not agree on the qualitative and quantitative features of an assessed risk that would result in its characterization as significant or not. Such an effort would take the federal agencies one step further toward dealing with risk information in a consistent and predictable way. It would also assist the desirable goal of avoiding sole reliance on highly uncertain quantitative estimates of risk.

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REFERENCES

ALBERT (1983). Discussion. *J. Amer. Pollut. Control Assoc.* **33,** 836–837.

COTTER, D. M. (1986). Work-related deaths in 1984: BLS survey findings. In *Monthly Labor Review,* pp. 42–44. U.S. Department of Labor. Bureau of Labor Statistics. May, 1986.

Environmental Protection Agency (EPA) (1979). Dibromochloropropane (DBCP): suspension order and notice of intent to cancel. *Fed. Regist.* **44,** 65135–65179.

Environmental Protection Agency (EPA) (1981). Federal radiation protection guidance for occupational exposures; proposed recommendations, requests for written comments, and public hearings; proposed recommendations for radiation protection of workers. *Fed. Regist.* **46,** 7836–7844.

Environmental Protection Agency (EPA) (1982a). Benomyl and thiophante-methyl: Determination concluding the rebuttable presumption against registration and availability of position document. *Fed. Regist.* **47,** 46747–46756.

Environmental Protection Agency (EPA) (1982b). Ethylene bisdithiocarbamates (EBDC'S): Determination concluding the presumption against registration; notice of availability of decision document; notice of determination; notice of availability. *Fed. Regist.* **47**, 47669–47674.

Environmental Protection Agency (EPA) (1982c). Trifluralin; determination concluding the rebuttable presumption against registration; notice of availability of position documents; notice of determination; notice of availability. *Fed. Regist.* **47**, 33777–33784.

Environmental Protection Agency (EPA) (1983). Ethylene dibromide; intent to cancel registrations of pesticide products containing ethylene dibromide; determination concluding the rebuttable presumption against registration; availability of position document; notice of intent to cancel; notice of availability. *Fed. Regist.* **48**, 46234–46248.

Environmental Protection Agency (EPA) (1984a). Tolerances for pesticides in food administered by the Environmental Protection Agency; animal drugs, feeds, and related products; tolerances for pesticides in animal feeds; dicamba; denial of stay. *Fed. Regist.* **49**, 47481–47483.

Environmental Protection Agency (EPA) (1984b). Cyromazine; proposed tolerance; proposed rule. *Fed. Regist.* **49**, 18120–18125.

Environmental Protection Agency (EPA) (1984c). Creosote, pentachlorophenol, and inorganic arsenicals; intent to cancel registrations of pesticide products containing creosote, pentachlorophenol (including its presumption against registration of the wood preservative uses of pesticide products); availability of position documents; notice of intent to cancel; notice of determination; notice of availability of position document. *Fed. Regist.* **49**, 28666–28689.

Environmental Protection Agency (EPA) (1984d). National emission standards for hazardous air pollutants; benzene emissions from maleic anhydride plants, ethylbenzene/styrene plants, and benzene storage vessels; proposed withdrawal of proposed standards. *Fed. Regist.* **49**, 8386–8391.

Environmental Protection Agency (EPA) (1984e). National emission standards for hazardous air pollutants; regulation of radionuclides; proposed withdrawal of proposed standards. *Fed. Regist.* **49**, 43906–43915.

Environmental Protection Agency (EPA) (1985a). Thiodicarb; pesticide tolerance; proposed rule. *Fed. Regist.* **50**, 18120–18125.

Environmental Protection Agency (EPA) (1985b). National primary drinking water regulations; synthetic organic chemicals, inorganic chemicals and microorganisms; proposed rule. *Fed. Regist.* **50**, 46936–47022.

Environmental Protection Agency (EPA) (1986a). *Superfund Public Health Evaluation Manual.* Office of Emergency and Remedial Response. EPA 540/1-86-060 OSWER Directive 9285.4-1. October, 1986.

Environmental Protection Agency (EPA) (1986b). Environmental Protection Agency National Primary Drinking Water Regulations. In *Code of Federal Regulations.* 40 CFR 141.

Food and Drug Administration (FDA) (1973). Compounds used in food animals; proposed rule. *Fed. Regist.* **38**; 19226–19230.

Food and Drug Administration (FDA) (1977). Chemical compounds in food-producing animals; criteria and procedures for evaluating assays for carcinogenic residues in edible products of animals. *Fed. Regist.* **42**, 10412–10437.

Food and Drug Administration (FDA) (1979a). Chemical compounds in food-producing animals. *Fed. Regist.* **44**, 17070–17114.

Food and Drug Administration (FDA) (1979b). Polychlorinated biphenyls (PCB's); reduction of tolerances; final rule. *Fed. Regist.* **44**, 38330–38340.

Food and Drug Administration (FDA) (1980). Lead acetate; listing as a color additive in cosmetics that color the hair on the scalp; final rule. *Fed. Regist.* **45**, 72112–72115.

Food and Drug Administration (FDA) (1982). D&C Green No. 5; final rule. *Fed. Regist.* **47**, 24278–24284.

Food and Drug Administration (FDA) (1985). Cosmetics; proposed ban on the use of methylene chloride as an ingredient of aerosol cosmetic products. *Fed. Regist.* **50**, 51551–51559.

Industrial Union Dept. v. American Petroleum Institute; 448 U.S. 607 (1980a).

Industrial Union Dept. v. American Petroleum Institute; 448 U.S. 607 (1980b), 65 L.Ed. 2nd 1043.

MANTEL, N., AND BRYAN, W. (1961). "Safety" testing of carcinogenic agents. *J. Natl. Cancer Inst.* **27**, 455–470.

National Research Council (NRC) (1983). *Risk Assessment in the Federal Government: Managing the Process.* Committee on the Institutional Means For Assessment of Risks to Public Health. National Academy Press, Washington, DC.

Nuclear Regulatory Commission (NRC) (1986). Standards for protection against radiation; republication. *Fed. Regist.* **51,** 1092–1216.

Occupational Safety and Health Administration (OSHA) (1983a). Occupational exposure to inorganic arsenic; supplemental statement of reasons for the final rule. *Fed. Regist.* **48,** 1864–1903.

Occupational Safety and Health Administration (OSHA) (1983b). Occupational exposure to ethylene dibromide; notice of proposed rulemaking. *Fed. Regist.* **48,** 45956–45975.

Occupational Safety and Health Administration (OSHA) (1984). Occupational exposure to ethylene oxide; final standard. *Fed. Regist.* **49,** 46936–47022.

Occupational Safety and Health Administration (OSHA) (1985). Occupational exposure to benzene; proposed rule and notice of hearing. *Fed. Regist.* **50,** 50512–50586.

Occupational Safety and Health Administration (OSHA) (1986). Occupational exposure to asbestos; final rule. *Fed. Regist.* **51,** 22612–22647.

RODRICKS, J. E., AND POHLAND, A. E. (1982). Food hazards of natural origin. In *Food Safety* (H. R. Roberts, Ed.), pp. 181–237. Wiley, New York.