LETTERS

Formaldehyde Regulation

Heads, more regulation wins; tails, less regulation loses. How do Ashford, Ryan, and Caldart (Articles, 25 Nov., p. 894) arrive at this self-protecting doctrine? If regulation is justified by scientific studies, it should proceed; if regulation lacks an adequate scientific component, it is still justified by something called science policy—apparently a political decision to make do with less than compelling evidence. But if the evidence is not up to scientific standards, or if there is not scientific agreement on the meaning of the evidence, it makes no sense to simultaneously charge the Environmental Protection Agency (EPA) and Occupational Safety and Health Administration (OSHA) with violating proper scientific practice where none exists. The muddle is made complete by such phrases as "scientific opinion on science policy," for if science policy is political, there cannot be a scientific opinion.

Only in this never-never world would it be possible to suggest that a particular decision conform to prevailing (although, quite possibly, changing) opinion among scientists without considering the implications. Would the authors of "Law and science policy in federal regulation of formaldehyde" support the positions taken by a majority of scientists? Or would we hear, as in regard to nuclear energy, where most scientists believe safety concerns to be exaggerated, that scientists are not elected and that "science policy" must take precedence?

I had not expected to read in *Science* a repudiation of the Fifth Circuit Court's restatement of the adage that "it is not good science to rely on a single experiment." Evidently the Court is guilty of neglecting or rejecting "science policy," relying instead "on its own understanding of scientific methodology." Is it, then, good science to rely on a single experiment? "The question," the authors write, "is . . . how many lives can be saved by regulating formaldehyde exposure?" Put this way—as life or death—the question contains its own answer. If it were recognized that a decision to regulate might also cause comparable harm—from the substance that takes the place of the regulated item, from loss of jobs, from an increase in uncertainty and anxiety—the losses and gains would have to be compared. Or is it good science policy to pick the first negative study that comes along without considering the harm that basing regulation on false positives can do? Or do the authors, as they accuse EPA and OSHA of doing, not only lead with their conclusions but arrange shifting criteria—science or science policy—so they cannot be refuted?

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Ashford *et al.* quote the report of the Federal Formaldehyde Panel ("formaldehyde should be presumed to pose a carcinogenic risk to humans") in juxtaposition with supposedly resultant actions on the part of EPA, OSHA, and the Consumer Product Safety Commission (CPSC). Later the authors conclude that the Toxic Substances Control Act (TSCA) equates "significant risk" with "only the possibility of a probable occurrence." This is used to support the authors' erroneous contention that (i) a 10 February 1982 concurrence (not "decision") memorandum written by me in support of a staff recommendation not to invoke section 4(f) of TSCA with respect to formaldehyde ignored evidence that formaldehyde could pose a carcinogenic risk to humans and; (ii) that all carcinogenic risks are equally significant regardless of magnitude (which I will refer to as the authors' "possible probability" standard for significance of risk).

With respect to the first point, the authors are demonstrably wrong, as the 10 February memorandum states quite plainly,

> One can therefore conclude . . . under certain exposure conditions it [formaldehyde] could present some carcinogenic risk to humans; and (d) given available data the risk estimates suggest that certain populations may experience a carcinogenic risk—albeit low—due to formaldehyde exposure.

Clearly, the memorandum did allow for the possible existence of human risk. Ashford *et al.* cite the Federal Formaldehyde Panel out of context and do not note that the panel did not address itself to the magnitudes of risks that might be present or whether such risks were worth emergency regulation [which is what TSCA section 4(f) involves]. The panel only addressed the issue of whether or not risk of any magnitude might exist. On that point there is no disagreement between the Federal Formaldehyde Panel report and the 10 February memorandum.

Ashford *et al.* appear to assume that all risks are of equal significance. In science, however, significance (in its nonstatistical sense) denotes the probability of observation, not the possibility of probability. In other words, possibilities may exist whose presence or absence does not materially affect a real world outcome; such are said to be nonsignificant. Not all possible cancer risks, when compared to other cancer risks, are significant. The 10 February memorandum addressed primarily the relative magnitudes of possible risks, as the possibility of such risks was already acknowledged. In the memorandum it was concluded that most such risks were not significant. Of exposure scenarios within EPA jurisdiction, a specific pesticidal use of formaldehyde appeared to pose high risks (such uses are specifically excluded from TSCA control). That use has since been modified (at my direction) by EPA's Office of Pesticide Programs. EPA continues on a reasoned regulatory review of formaldehyde, a review initiated by me in a different 10 February memorandum, "OTS Formaldehyde Workplan" (a memorandum Ashford *et al.* do not mention).

How the authors arrive at a "possible probability" standard for significance of risk is difficult to understand from a toxicological point of view. For nearly 500 years the Paracelsian principle of dose-response has served as a cornerstone of the toxicological sciences. The authors' viewpoint requires that one reject this fundamental principle of dose-response. Only in this way can all risks become equal and, therefore, equally significant.

Ironically, the principle of dose-response lies at the heart of risk management under TSCA [and several other federal statutes (*1*)]. Under these statutes, EPA has generally regulated carcinogenic risks by reduction of excessive exposures to levels that result in lowering of risks to within a range considered to be insignificant or de minimis and below which further risk reduction is seldom considered to be productive. This recognizes the fact that risk, or response, is a function of exposure, or dose. Such an approach defines three classes of risks: those that do not exist; those that exist but have no practical effect; and those that exist and have a practical effect (that is, are significant). The Ashford *et al.* "possible probability" standard defines only those risks that are possible and those that are not. Such an approach, as a practical matter, is of no use to a real-world regulatory agency that must make decisions on allocation of resources and efforts in risk management.

Ashford *et al.* also ascribe a "reliance on methodologically inadequate epidemiological studies" to the 10 February

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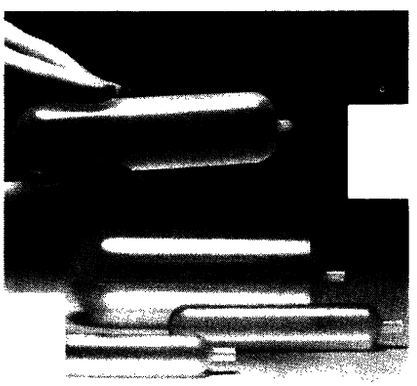

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memorandum. The entire issue of epidemiology is dealt with in one short paragraph in a 16-page memorandum, and the text shows that the authors are not correct.

While I recognize the limits of sensitivity inherent in epidemiology, such data are useful. In particular, for chemicals of long standing and well defined use, epidemiology could tell if a critical situation exists. If formaldehyde were a potent human risk, this would show up epidemiologically. There does not appear to be any relationship, based on the existing data base for humans, between exposure and cancer. Real human risk could be considered to be low on such a basis.

The text clearly states that, while the epidemiology does not rule out the existence of a low-level risk, neither does it support the existence of a high level of risk. The only passing consideration given this issue in a lengthy memorandum indicates that it was neither a critical nor central issue.

Ashford *et al.* further state that "incoming EPA officials had determined their policy on formaldehyde long before any 'decision-making process' had been completed. . . . J. Todhunter himself has testified that when he arrived at EPA in July 1981 he was informed that the agency would take no regulatory action on formaldehyde." This testimony refers to discussion (concerning the career staff's view regarding emergency regulation of formaldehyde) with Warren Muir, then head of EPA's Office of Toxic Substances. Muir was a career employee in charge of TSCA administration and most certainly not an "incoming official," as he had been head of the Office of Toxic Substances at EPA under the Carter Administration.

Ashford *et al.* also state that, on the basis of "substantial" but unspecified evidence, "Todhunter met on several occasions with John Byington, attorney for the Formaldehyde Institute, and Len Guarraia, then a director of the American Industrial Health Council." The record (*2*) has well established that such meetings with these gentlemen—the latter of whom was not even professionally involved with formaldehyde—did not occur when the 10 February memorandum was being prepared. Unfortunately for all so maligned, the "substantial" evidence relied on by the authors is a supposed—but highly inaccurate—list of "meetings" compiled by former congressional staffer Lester O. Brown. Brown has since left the employ of Congress after admitting to being responsible for improper alteration of transcripts of EPA oversight hearings held in the summer of 1982 (*3*).

The authors' views are at odds with those of interested federal agencies (save CPSC) regarding formaldehyde and with court decisions on this substance (*4*). It is, of course, the authors' prerogative to disagree. The errors noted above do not, however, build a strong case for the authors' point of view.

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Ashford *et al.* argue that, in the areas where the law is unspecific or science uncertain, it is established practice to use "science policy"—a body of prudent assumptions and decision strategies for handling insufficient data—to fill the gap. Such a body of received assumptions has come into being for the regulatory treatment of carcinogens, and Ashford *et al.* charge that EPA administrators under President Reagan have sought to change this existing "science policy" without valid scientific reasons, and also without adequately exposing whatever justification they thought they might have to review by scientists and the public.

The latter criticism is unfortunately valid and is emblematic of the general unease shown by the Reagan Administration in dealing with the scientific and technical community. But the former criticism is arguable. "Science policy" is derived, after all, for the general case, and it does not seem wise to blindly apply its settled assumptions where evidence is available casting doubt upon or flatly contradicting them. Such is the case with formaldehyde.

1) Formaldehyde, unlike most carcinogens identified in animal cancer tests, is not a synthetic industrial chemical but a normal metabolite in human biochemistry with an elaborate enzymatic system already in place for handling it. This suggests that our bodies are capable of handling it safely as long as exposure is not much higher than the amounts the body itself manufactures.

2) Such enzyme systems are, like enzymes in general, saturable, which im-

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plies that harmful effects (including cancer) seen at high, saturating doses almost certainly cannot be manifest in proportion at low, physiologically normal doses. In fact, the Chemical Industry Institute of Technology inhalation study in rats shows just this behavior. The incidences and doses were as follows for squamous cell carcinoma of the nasal passages, the only tumor seen in significant numbers (males and females calculated together): 0 of 232 at 0 part per million (ppm), 0 of 236 at 2.0 ppm, 2 of 235 at 5.6 ppm, and 103 of 232 at 14.3 ppm (*1*). This is a solidly nonlinear dose response of high order, and it shows that the standard practice of assuming, when data are lacking, a linear dose response for purposes of human risk estimation is clearly inappropriate here. (Science policy is, after all, supposed to fill gaps, not override available data.)

3) Mice, when tested in parallel under identical conditions with comparable numbers of animals at risk, did not develop a significant incidence of tumors of any sort. It is true that the general "science policy" presumption has been that even "well conducted" negative animal studies "will not be said to detract from well-established positive evidence for other species," and this is defensible when one tries to make sense out of a large mass of wayward bioassay data carried out in many different laboratories with differing degrees of statistical power and with nonuniform methods of tumor classification. But this general presumption is validly controvertible in cases where, as here, the doses, exposure times, statistical sensitivity, and criteria for tumor evaluation are perfectly comparable in the two bioassays. The only salient difference between the two tests is the choice of species, and hence the discordant results between two taxonomically close relatives tested under identical conditions does raise the question of how much confidence we are obliged to place in generalizing the cancer verdict in rats to the taxonomically quite distant species called humans.

Given that formaldehyde is as ubiquitously useful as it is, wise regulatory rule-making would not, I believe, apply "science policy" so rigidly as to override the above facts. But such a clear departure from accepted practice should, without doubt, be aired before the scientific community and the public.

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In Wildavsky's letter, the nature of science, science policy, and procedural consistency in decision-making are confused. He sets up "straw men" and attributes to us positions that we do not take.

We argue neither for nor against more regulation. Rather we criticize OSHA and EPA for departing from their previously articulated positions on matters of science policy without following the proper administrative procedures for doing so. Further, we criticize the Fifth Circuit Court of Appeals for violating the principles of judicial review by substituting its own judgment on issues of science policy for that of the CPSC.

Nor do we suggest that science policy provides agencies with carte blanche to regulate at will. In situations where an agency's statutory mandate requires it to make regulatory decisions in the face of scientific uncertainty, however, the agency will necessarily be making science policy determinations. As the courts have long recognized, basing regulatory action on science policy determinations violates neither good science nor good law. While proper identification and understanding of issues of science policy demand a working knowledge of the underlying scientific principles, the ultimate resolution of these issues must rest on determinations of social policy. The formulation of social policy, within the confines of a congressional mandate, is precisely the function society has assigned to the regulatory agencies.

Finally, we do not, as Wildavsky suggests, argue that an agency is bound to accept the views of scientists on questions of science policy. Our position is simply that when a majority viewpoint on a science policy issue has evolved within the relevant scientific community, the agency should not depart from that viewpoint without acknowledging its departure and articulating a reasoned justification for taking a contrary view. The role of the courts is to ensure that the agency's position on such issues—whether or not consistent with that of the scientific community—is arrived at by a reasoned decision-making process.

Todhunter's comments are inconsistent with our article, with his own prior statements, and with the TSCA. We address them in the order presented.

Certainly, we do not contend that Todhunter ignored *all* evidence of formaldehyde carcinogenicity in his memorandum of 10 February 1982. Our article does state, however, that this memorandum failed to address certain key empirical data contrary to its author's assessment of the significance of the human

cancer risk posed by exposure to formaldehyde. We, and others, have documented these factual omissions in detail in other publications (*1, 2*).

We do not contend that Todhunter's memorandum wholly ignores the possibility that formaldehyde poses a significant cancer risk to humans. Indeed, as we note in our article, Todhunter's own informal risk assessment—that "there may be human exposure situations . . . which may not present carcinogenic risk of significance"—necessarily implies the possibility of significant human risk.

Nor do we quibble with Todhunter's position that "significance" refers to "probability." Our article quite clearly states our opinion that "significance," in the context of section 4(f) of TSCA, "pertains to the likelihood of occurrence." We *do* quibble, however, with Todhunter's disregard of the word "may" in section 4(f). That section of TSCA is triggered whenever (*3*)

> there *may* be a reasonable basis to conclude that a chemical substance or mixture presents or will present a significant risk of serious or widespread harm to human beings from cancer [emphasis added].

In law, science, and everyday usage, "may" refers to possibility. As we suggest in our article, a threshold determination under section 4(f) may fairly be said to require only a "credible possibility" of significant risk. At this point, the agency is directed by the plain language of the statute to give serious, immediate consideration to the propriety of taking regulatory action under one or more of the various provisions of sections 4, 5, 6, and 7 of TSCA. If Todhunter disagrees with this framework, his quarrel is with Congress, not with us.

With regard to Todhunter's reliance on the then-available epidemiological studies of formaldehyde, we can only refer him back to his own language. That language—both in the 10 February memorandum and in his current response to our article—indicates that Todhunter treated these studies as evidence that the human risk of formaldehyde was not "critical," "potent," or "high-level." Yet a number of methodological inadequacies—such as small sample size and poor exposure documentation—renders them unsuitable for this purpose. Most evaluators, including the International Agency for Research on Cancer (IARC), the CPSC, and even EPA's own Office of Toxic Substances, declined to rely on the available epidemiology in their analysis of formaldehyde carcinogenicity (*1*).

Todhunter's suggestion that his initial EPA discussions on formaldehyde were with Warren Muir appears to be at odds with his congressional testimony. In a hearing before Representative Florio's subcommittee, Todhunter testified as follows (*4*, p. 27):

> When I arrived at the agency, before I ever met with Dr. Hernandez, I was briefed by Dr. Mueller and Mr. Clark, who was at the time the acting assistant administrator, and was informed that the Agency at the time had no intention of regulating formaldehyde. . . ."

Had the discussions been with Muir, one would think that Todhunter's testimony would have reflected this fact. Indeed, the Office of Toxic Substances, when headed by Muir, had recommended that section 4(f) be deemed to have been triggered for formaldehyde.

Similarly, Todhunter's statements regarding meetings with Byington and Guarraia are difficult to reconcile with his congressional testimony. In response to questioning from Representative Moffat, Todhunter testified that "I know I had breakfast with Mr. Byington at least once, possibly twice during January" (*4*, p. 29), only days before the completion of the 10 February memorandum. Further, the same congressional testimony indicates that a "planning calendar" *submitted by Todhunter* lists several scheduled meetings with Guarraia in December, January, and early February. If these meetings were merely the product of a staffer's overactive imagination, that fact is certainly not evident from Todhunter's testimony. Guarraia was then a director of the American Industrial Health Council (AIHC) and director for government relations for the Synthetic Organic Chemical Manufacturers Association (SOCMA). Both AIHC and SOCMA have strong ties to the Formaldehyde Institute. AIHC is an industry research and lobbying group and, until 1979, the Formaldehyde Institute was part of SOCMA, where it was known as SOCMA's "Formaldehyde Task Force." All three organizations maintain their offices in Scarsdale, New York, and as of April 1983 shared the same phone number (*1*).

Finally, Todhunter's reliance on a Massachusetts Superior Court decision [his reference (*4*)] is ill founded. While a Superior Court judge did overturn the state's ban on urea-formaldehyde foam insulation in 1982, the Massachusetts Supreme Judicial Court reversed the lower court's decision in April 1983 and reinstated the ban on the use of urea-formaldehyde foam insulation (*5*).

Havender raises technical issues regarding the scientific determination of formaldehyde's carcinogenicity and risk assessment. We did not in our article express our opinion on this subject—we focused on legal process and science policy concerns. However, Havender's

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technical arguments represent just the sort of plausible-sounding but superficial analysis that might prevail in an unscrutinized administrative decision process, but which would be unlikely to survive in the critical public and judicial review that would accompany formal proposals to alter EPA science policy on carcinogens.

Havender starts with the general point that formaldehyde "is not a synthetic industrial chemical but a *normal* metabolite in human biochemistry" (emphasis added) and that therefore "This suggests that our bodies are perfectly capable of handling it safely as long as exposure is not much higher than the amounts the body itself manufactures." Use of the word "safe" incorrectly implies that the natural enzymatic and other defenses against formaldehyde's DNA-damaging action are likely to be "perfectly" efficient at usual formaldehyde concentrations in human tissues. In fact, although the series of defenses may be quite good, there is no possible way it can be perfect. As long as there is a finite concentration of enzyme molecules that can metabolize formaldehyde and a finite series of membranes providing barriers to diffusion, then some finite fraction of "natural" formaldehyde molecules will reach DNA and react with it. Then, as long as there is a finite number of DNA repair enzyme molecules and a finite time for them to work before the next cell replication, some finite fraction of initially generated DNA lesions will persist to the time of DNA copying, when they can induce permanent changes in the stored information. Over the course of evolution it is likely that some rough balance has been struck between the biological costs of formaldehyde's damage and the biological costs of increasing internal defenses against formaldehyde, but there is no chance that the damage has been entirely eliminated. Human beings do not live in a Garden of Eden, either externally [as was illustrated extensively recently by Ames (*6*)] or internally. That "natural" chemicals and radiation are perfectly capable of a continuing production of "natural" damage to our genetic apparatus (with occasionally disastrous results to individuals), and have undoubtedly been doing so since the dawn of biological history, is no reason to suggest that additional amounts of such chemicals or radiation can be tolerated without additional biological cost and risk. One simply cannot identify "natural" with "safe."

Havender's second technical paragraph correctly notes that at high doses the rat squamous cell carcinoma response is nonlinear. This does not invalidate and is not in any way inconsistent with, standard approaches for assessing carcinogenesis risk at low doses. The most common procedure of Crump (*7*) and EPA's Carcinogen Assessment Group (*8*) is designed to accommodate just such data and calculate upper confidence limits for low-dose risk on the assumption that the high-dose nonlinearities are produced by the need for normal cells to undergo a series of stages before becoming tumors, several of which may be affected by the carcinogen. These upper confidence limits turn out to be linear because, in general, one cannot exclude the possibility that there is a small contribution from a linear, one-stage process.

Havender's further argument on linearity suggests that even "best estimate" carcinogenesis dose-response functions should be linear at low doses for agents that act by primary reaction with DNA. As we have discussed at length elsewhere (*9*), there are many processes that can give rise to nonlinearities at high doses (saturation of transport processes, induction or saturation of activating or inactivating enzyme systems, induction or saturation of "error prone" or "error free" DNA repair systems, and multiple-mutation pathways of carcinogenesis). However, it is clear from a careful mathematical analysis that, as long as the basic mechanism of action of the carcinogen is by primary reaction with DNA, nonlinearities of the saturation or induction type must necessarily disappear at low doses. Basically this is because saturable Michaelis-Menton enzyme kinetic and transport processes become linear at low doses:

$$-d[S]/dt = V_{max}[S]/(K_m + [S] = \sim \text{low } [S]V_{max}[S]/K_m$$

where $[S]$ is the concentration of the saturation, V is velocity, and K_m is the Michaelis constant. Even the nonlinearity that is due to the need for multiple mutations to turn a normal cell into a fully malignant tumor will disappear at low doses so long as there is a finite "background" rate of each of the transitions in the sequence. The basic conclusion must be that, even though a best estimate slope for a carcinogenic dose-response relation can be very different at low doses from that at high doses (and in the case of formaldehyde, the low-dose slope is likely to be much shallower), there is every reason to suppose that the basic form at low doses should be linear for carcinogens that act at least in part by primary reaction with DNA.

Havender's final point, that the mouse experiment somehow casts doubt on validity of the rat data, is equally spurious. First, it is hardly fair to call the mouse results "discordant" with the findings in rats on the basis that the mice did not show a "significant" response. Even though only two squamous cell carcinomas were observed in the highest dose mouse group (versus none in the other groups) when three would have been required for statistical "significance" at the 5 percent level, the qualitative similarity in the findings of an otherwise very rare tumor type if anything reinforces the rat experiment. Further, as has been pointed out by the Chemical Industry Institute of Toxicology itself (*10*), mice decrease their respiration more than rats in response to high irritating concentrations of formaldehyde. When one compares the observed response in the two species on the basis of the actual dose of formaldehyde effectively delivered per unit surface area, as we did in our formaldehyde risk assessment (*11*), the observed mouse data are fully consistent with the response observed in rats.

It is not unlikely that there are cases where, after due reflection, the preexisting science policy principles of EPA and the Interagency Regulatory Liaison Group for assessing risk from carcinogens (*12*) may need to be modified. Formaldehyde, however, does not appear to be such a case.

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