Jupiter. Shown in Fig. 9 is an early map of Jupiter made by Roberts *et al.* (*8*). The thermal emission from the central disk of the planet is clearly perceptible, and surrounding it is the nonthermal radio emission from Jupiter's radiation belts. These structures are analogous to the Van Allen radiation belts around the earth.

Observations of radio events on the sun with the VLA have been carried out by groups from the California Institute of Technology, the University of Maryland, Tufts University, and others. With the high resolution and high frequencies of the VLA solar radio astronomers can observe deep into the solar atmosphere to see radio emission associated with the sites of origin of major flares. A VLA radio map of a solar active region obtained by Velusamy and Kundu (*9*) is shown in Fig. 10. The radio contours are superimposed on an optical photograph in the hydrogen alpha line taken by R. Robinson at Sacramento Peak Observatory.

Among the many complex problems being investigated by solar radio astronomers with the VLA, there is one specific theme that occurs with great frequency. With the VLA one can make very good, high-resolution maps of potential flare sites. This makes it possible to locate and study radio emission from material participating in the motions and acceleration processes involved in the conversions of energy between magnetic fields and plasma which are basic to the physics of active regions and flare sites.

A final example of the use of the VLA in solar system studies is the observation of asteroids. C. M. Wade, K. J. Johnston, and P. K. Seidelmann are using the VLA to observe and track Ceres and other asteroids. This is one of few cases where both radio and optical emission are due to exactly the same (thermal) processes in the same physical regions. Thus successful simultaneous tracking of asteroids with the VLA and optical astrometric telescopes will allow the radio and optical observing reference frames to be established with respect to each other to high accuracy.

Future of Astronomy with the Very Large Array

In the survey above I have had to neglect the vast majority of scheduled VLA observing programs. An outline of these programs summarizes the expected role of the VLA in the coming decades. I have not discussed observations of comets, moons around solar system planets, ordinary stars, double stars, flare stars, pulsars, gaseous nebulas, novas, supernovas, supernova remnants, x-ray sources, interstellar molecules, interstellar neutral hydrogen, the structure of nearby spiral galaxies, supernovas and gaseous nebulas in other galaxies, or the full variety of radio phenomena in other radio galaxies and quasars. All of these have been and will continue to be observed by astronomers using the VLA. For astronomical observations at centimeter wavelengths and resolutions from 0.05 arc second to a few arc minutes, the VLA will probably continue to be the dominant instrument for at least the next two decades.

References and Notes

1. A. R. Thompson, B. G. Clark, C. M. Wade, P. J. Napier, *Astrophys. J. Suppl.* **44**, 151 (1980).
2. J. Burns and W. Christiansen, *Nature (London)* **287**, 20 (1980).
3. S. P. Ewald, thesis, New Mexico Institute of Mining and Technology (1981).
4. R. T. Newell, thesis, New Mexico Institute of Mining and Technology (1981).
5. R. M. Hjellming and K. J. Johnston, *Astrophys. J. Lett.* **246**, L141 (1981).
6. B. Mangon, *Science* **215**, 247 (1982).
7. P. Bowers, K. J. Johnston, J. Spencer, *Astrophys. J.*, in press.
8. J. Roberts, G. Berge, R. C. Bignell, in preparation.
9. T. Velusamy and M. R. Kundu, in *Radio Physics of the Sun*, M. R. Kundu and T. Gergely, Eds. (Reidel, Boston, 1980), pp. 105–108.
10. The National Radio Astronomy Observatory is operated by Associated Universities, Inc., under contract with the National Science Foundation.

Formaldehyde: A Question of Cancer Policy?

Frederica Perera and Catherine Petito

In what may constitute a test case for a new federal cancer policy, the Formaldehyde Institute, an association of formaldehyde producers and users, has advocated that formaldehyde not be regulated by the federal government despite recent studies showing that the substance causes tumors in animals and despite evidence that there is considerable human exposure to formaldehyde. The institute has argued that the animal data do not provide a sufficient basis to regard formaldehyde as a likely human carcinogen and that federal regulatory agencies should await the development of conclusive human (epidemiological) data before taking protective action.

This position contradicts principles for assessing carcinogenic risk that have been widely accepted by the scientific community for over a decade and embodied in policies of regulatory agencies following deliberations of broad-based scientific panels. These principles assert that confirmed positive animal data are presumptive evidence of carcinogenicity in humans; that with current information and methods it is not possible to establish threshold or no-effect levels that can be reliably applied to the human population; and that positive human epidemiological data are not necessary to conclude that a chemical substance poses a significant human risk (*1*). In fact, federal agencies have regulated such substances as pesticides, hair dyes, food additives, and industrial carcinogens (for example, β-propiolactone and ethyleneimine) in the workplace primarily on the basis of results in experimental animals (*2*). These principles are consistent with the accepted social policy that it is preferable to err on the side of caution in interpreting the available scientific data in order to avoid failure to regulate a serious health hazard.

Thus, acceptance by federal agencies of the industry position regarding the risk posed by exposure to formaldehyde could overturn established procedures for assessing and regulating carcinogenic

Frederica Perera is a senior staff scientist at the Natural Resources Defense Council, New York 10168, and assistant clinical professor, Division of Environmental Health Sciences, Columbia University School of Public Health. Catherine Petito is a science associate at the Natural Resources Defense Council, New York 10168.

0036-8075/82/0618-1285$01.00/0

Summary. This article describes recent events concerning the assessment and regulation of formaldehyde, and evaluates the scientific data pertaining to the carcinogenicity of this substance in the context of established cancer policies and guidelines. The conclusion is that recent decisions by several federal agencies to defer action to limit human exposure to formaldehyde may be a "test case" for a new, less protective policy concerning the regulation of carcinogenic substances in general.

substances in general. During the last 8 months, Environmental Protection Agency (EPA) and Occupational Safety and Health Administration (OSHA) officials have reversed prior staff recommendations to initiate regulatory action to limit human exposure to formaldehyde (*3–5*). In February 1982, EPA declined to regard formaldehyde as a priority candidate for regulation under the Toxic Substances Control Act (TSCA) on the basis that the animal data may not be relevant to humans, that there is an absence of positive human data, and that it has not been established that, at human exposure levels, the risk of cancer is "probable and would be high" (*6*). According to sources quoted in *Inside EPA*, not only does the agency's decision not to move quickly on formaldehyde reflect a "clear divergence from current federal policy," but "EPA Deputy Administrator John Hernandez has made tentative plans to totally revamp the agency's cancer policy." (*4*).

Our purpose in this article is to review in detail the data on the carcinogenicity of formaldehyde in light of established guidelines for assessment of carcinogenic substances to see the extent to which the recent federal agency decisions represent a major policy change.

Background

Formaldehyde (HCHO) is a versatile chemical used in the manufacture of such products as particle board, plywood, paper, home insulation, material polymers and resins, leather and agricultural products, permanent-press fabrics, preservatives, embalming fluids, drugs, and cosmetics. About 7 billion pounds of formaldehyde are produced each year, making it the 26th largest volume chemical in the United States (*7*). An estimated 1.4 million people are exposed to formaldehyde in the workplace; 11 million people may breathe vapors in the home released by construction and insulation materials; and virtually the entire population comes into contact with the chemical because of its ubiquitous presence in polluted air and in consumer products (*8*). Concentrations of more than 8 parts per million (*9*), 0.02 to 4.2 ppm (*8*), and 0.1 to 3.4 ppm (*10*) have been measured in the workplace, in mobile homes, and in U.S. houses insulated with urea-formaldehyde foam, respectively, while levels frequently range above 0.1 ppm in urban air (24-hour average) (*8*). The present U.S. occupational standard for formaldehyde is 3 ppm (time-weighted 8-hour average) (*11*).

Thus, in the fall of 1980 there was widespread recognition of the significance of an interim report from the Chemical Industry Institute of Toxicology (CIIT) that formaldehyde was carcinogenic in rats (*12*). According to the final report (*13*), at the end of a 30-month period squamous cell nasal carcinomas were observed in 103 of 232 rats exposed by inhalation to 14.3 ppm of formaldehyde, in 2 of 235 rats exposed to 5.6 ppm of formaldehyde, and in 2 of 225 mice exposed to 14.3 ppm of formaldehyde. No such nasal cancers were found in 236 rats exposed to 2 ppm of formaldehyde or in the control animals. Polypoid adenomas were reported in all exposure groups and in one male control rat. By February 1981, various groups of experts had reviewed the CIIT interim (*7*) data, including a federal panel convened at the request of the Consumer Product Safety Commission (CPSC) under the aegis of the National Toxicology Program (NTP) (*14*) and the Environmental Cancer Information Unit of the Mount Sinai School of Medicine (*15*). The NTP report stated that "Formaldehyde should be presumed to pose a risk of cancer to humans" in agreement with the Mount Sinai conclusion that

> HCHO is a carcinogen in rats and, data suggest, in mice at exposure levels comparable to those found in some home and work environments. These findings indicate that effective controls should be initiated to reduce or eliminate human exposure to HCHO [*15*, p. 9].

Meanwhile, experiments at New York University (NYU) (*16, 17*) showed that exposure of groups of 100 male rats to formaldehyde and hydrogen chloride separately and combined, at average concentrations of 14 ppm and 10 ppm, respectively, resulted in an excess of histologically confirmed nasal squamous cell carcinomas in rats exposed to HCHO alone and none in the controls or in the rats exposed to HCl alone. Combined exposure to HCHO and HCl produced about the same number of histologically confirmed nasal squamous cell carcinomas as HCHO alone (*16*). As in the CIIT study, no grossly visible spontaneous nasal tumors of this type had been observed in control rats at that laboratory over a period of many years (*17, 18*).

In the spring of 1981, on the basis of the CIIT study and a review of available data on formaldehyde use and human exposure to the chemical (*19*), EPA staff drafted a *Federal Register* notice under §4(f) of TSCA designating formaldehyde as a priority chemical for regulatory assessment (*20*). The draft 4(f) notice stated:

> EPA has determined that there may be a 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 [*20*].

The notice was not signed by the Administrator of EPA. Rather, during the summer of 1981 EPA Deputy Administrator John Hernandez convened a series of unannounced meetings—termed "science courts"—primarily attended by EPA and Formaldehyde Institute representatives in order to review the scientific data on formaldehyde (*21*). A congressional subcommittee was critical of this significant departure from the accepted peer review process (*3, 22*).

On 4 September 1981, the Natural Resources Defense Council (NRDC) requested an explanation of EPA's failure to act on formaldehyde under §4(f) of TSCA and notified the agency of its intention to seek judicial review of that failure under §20 of the act. On 11 September 1981, a memorandum from Don Clay, Office Director of the EPA Office of Toxic Substances (OTS), to John Todhunter, then Assistant Administrator Designate for Pesticides and Toxic Substances, recommended against treating formaldehyde as a priority for assessment under §4(f) of TSCA pending additional epidemiological information (*23*).

In parallel developments at OSHA, in July 1981 an OSHA official recommended reversal of a prior decision to release a bulletin on formaldehyde jointly with the National Institute for Occupational Safety and Health (NIOSH) (*24*). The NIOSH *Current Intelligence Bulletin* had stated that formaldehyde should be

handled as a potential occupational carcinogen and that appropriate controls should be imposed to reduce worker exposure (*9*). OSHA also denied a 26 October 1981 petition by the United Auto Workers (*25*) for an emergency standard for formaldehyde. OSHA's action in putting aside new standards on formaldehyde and other substances triggered concern that new officials at OSHA were likely to revise the agency's cancer policy (*5*).

On 17 August 1981, Arthur Upton, Chairman of the NYU Medical Center Institute of Environmental Medicine, wrote to the heads of federal agencies that formaldehyde is "decisively carcinogenic in animals" and "if the carcinogenicity of formaldehyde is ignored, it would mean that no agent could be regarded as carcinogenic in the absence of positive evidence in humans" (*17*). This letter prompted a response from Joel Bender, Chairman of the Medical Committee of the Formaldehyde Institute, that "to regard formaldehyde as a likely carcinogen in man is not supportable" (*26*). By contrast, in October 1981 a working group of the International Agency for Research on Cancer (IARC) concluded, on the basis of the CIIT and NYU studies, that formaldehyde gas is carcinogenic to rats and should be considered "for practical purposes," in the absence of adequate data in humans, as if it represented a carcinogenic risk to man (*27*).

On 29 January 1982, a detailed letter to the assistant secretary for OSHA, the EPA administrator, and the chairman of the CPSC from Upton of NYU and I. B. Weinstein of Columbia University recommended prudent measures to restrict exposure to formaldehyde:

> It has come to our attention that EPA, OSHA, and possibly other federal regulatory agencies, may be planning not to take immediate protective action on formaldehyde, in spite of substantial evidence for its carcinogenicity from animal bioassays. We are concerned about the possibility of such a departure from established public health policy. It would conflict with the prevailing views of the scientific community and would set a precedent which could hamper future regulatory action on other carcinogens.
>
> There is general agreement among experts in chemical carcinogenesis that a substance which causes cancer in significant numbers of experimental animals in well-conducted assays poses a presumptive carcinogenic risk to some humans, even in the absence of confirmatory epidemiological data. While negative human data can define the upper limit of risk to man, there is no recognized method as yet for establishing the existence of a threshold for a carcinogen in the human population. These principles, which are accepted throughout the world, have served for many years as the basis for sound public health policy and regulatory action on carcinogens.
>
> To compare our views on this subject with those of our colleagues, we have consulted several of the world's leading authorities on chemical carcinogenesis for their opinions. The replies we have received from them thus far are unanimous in supporting the principle that definitive demonstration of carcinogenicity in well-conducted animal bioassays suffices to provide evidence of presumptive carcinogenicity for the human population [*28*].

A week later, the American Cancer Society issued a statement urging regulatory agencies "to set appropriate standards to minimize occupational and public exposure to the chemical, its industrial products and applications" (*29*).

On 10 February 1982, Todhunter, EPA Assistant Administrator for Pesticides and Toxic Substances, formally recommended against considering formaldehyde as a priority candidate for regulation. Characterizing formaldehyde as a "potential animal carcinogen" he observed that concern about human carcinogenicity should be "tempered" by the observations that

> quantitative and possibly qualitative results of exposure to formaldehyde appear to depend highly on exposure level, species, and route; that rats seem to be particularly sensitive to formaldehyde; and that long human experience does not seem to indicate any pressing concerns . . . [*6*].

By contrast, the CPSC voted on 22 February 1982 to ban urea-formaldehyde foam insulation (*30*). Canada and the states of Massachusetts and Connecticut had previously banned the use of urea-formaldehyde foam (*31*).

Validity of the Data

Questions have been raised about the validity of the animal data (*26*). However, the CIIT study (*13*) was rigorously peer-reviewed and is considered to be valid (*14, 15, 27, 32*).

The possibility of a viral respiratory infection confounding the data in the CIIT study was considered unlikely in the NTP and Mount Sinai reports (*14, 15*). Control animals had also shown signs of viral infection but did not develop tumors. Further, in some of the rats, nasal cancers had formed by the time respiratory viral infection occurred (*33*). In the NYU study confirming the CIIT findings, a sample of the animals was tested for the virus and found to be negative (*34*); in the CIIT study mice were not affected by the virus yet they developed tumors. Although it is unlikely that the transient viral infection contributed to the carcinogenic response of formaldehyde, people exposed to the chemical may also experience viral infections of the upper respiratory tract (*14, 15*). Addressing the criticism that the CIIT study is flawed because "ulcerative inflammatory lesions" were present in nasal mucosa, CPSC staff scientists have written that pathologists who examined the slides from the CIIT study did not observe such changes (*35*).

The NYU studies provide confirmation of the CIIT results in a different strain of rats (*16, 17*). According to Upton (*17*), the studies "provide decisive confirmation of the Chemical Industry Institute of Toxicology findings that formaldehyde induces squamous cell carcinoma in rats." Partly because the type of tumor was not that associated with bis(chloromethyl)ether (BCME), it is judged unlikely that the formation of BCME as a result of combination of formaldehyde and HCl was responsible for the excess squamous carcinomas in the nasal cavities (*9, 14, 36*). The fact that formaldehyde alone produced about the same number of tumors as when combined with HCl also argues against an etiologic role for BCME.

The prior reports of negative results in three long-term inhalation studies of formaldehyde do not detract from the significance of the CIIT and NYU studies. According to the NTP report (*14*), all three had shortcomings in experimental protocols and execution (for example, high mortality, inadequate exposure, or deficient histopathology). Bioassays in which other routes of exposure were used have been similarly limited; however, some give definite clues that formaldehyde may be carcinogenic to a variety of target tissues and animal species (*14*).

Formaldehyde Data in the Context of Established Cancer Policies

A number of principles have been elaborated in reports written during the last 10 years by various scientific committees concerning the assessment of human risk from environmental carcinogens. Composed of scientists affiliated with academic institutions, industry, and government, these committees were broadly representative of the scientific community. Their reports included those of the National Cancer Advisory Board, the Interagency Regulatory Liaison Group (IRLG), the National Research Council (NRC), the Food Safety Council, the Office of Technology Assessment (*1*), and the Occupational Safety and Health Administration (OSHA) as well as publications by the IARC and the

New York Academy of Sciences (*37–45*). Developed cooperatively by representatives of all federal agencies concerned with toxic substances control, the IRLG guidelines were based on an extensive review of the scientific literature on carcinogen assessment. EPA formally adopted (in 1979) the IRLG policy for purposes of evaluating evidence regarding suspect carcinogens as a supplement to its own Interim Guidelines for Carcinogenic Risk Assessment (*46, 47*). In particular, the report of the Toxic Substances Strategy Committee (TSSC) published in 1980 is significant because it was based on a review of 23 major reports written between 1956 and 1979 (*48*). The TSSC, composed of representatives from federal agencies with responsibility for controlling toxic substances, identified "principles and technical considerations underlying federal policies for the identification of potential human carcinogens":

> Although they have been the subject of considerable public misunderstanding, these principles are widely supported in the scientific community and in the deliberations of rulemaking and adjudicatory bodies, the courts, expert committees, and international agencies [*48*, p. 125].

Even more recently, the Office of Technology Assessment has reviewed and reaffirmed the basic principles of carcinogenicity assessment (*1*). These principles are as follows.

1) Animal testing data from properly designed and well-conducted tests are adequate for concluding that a chemical substance is a likely carcinogen in humans.

Over 30 chemicals or industrial processes are judged by the IARC to be carcinogenic or probably carcinogenic to humans on the basis of epidemiological evidence (*49*). Of those for which animal data exist, all (with two possible exceptions) have been positive in experimental animals. The two possible exceptions are benzene and arsenic. However, there is evidence from two recent bioassays that benzene is carcinogenic in animals and that arsenic may be a cocarcinogen capable of inhibiting DNA repair (*50, 51*). Hence, the IARC has concluded:

> In the absence of adequate data on humans, it is reasonable, for practical purposes, to regard such chemicals [for which there is sufficient evidence of carcinogenicity in animals] as if they presented a carcinogenic risk for humans [*52*, p. 14].

Thus:

> All Federal agencies accept a positive bioassay result in a single species as evidence that the substance is a potential human carcinogen [*1*, p. 13].

a) Animal testing at high dose levels is a valid and necessary procedure for identifying potential human carcinogens.

> The exposure of experimental animals to toxic agents in high doses is a necessary and valid method of discovering possible carcinogenic hazards in man [*39*, p. 7].
>
> Since carcinogenic response is usually dose related, the biological and statistical sensitivity of a bioassay may be enhanced by increasing the exposure levels of the test substances rather than the less feasible alternative of increasing the number of test animals to match the human population at risk [*42*, p. 5093].
>
> The basis for such extreme doses, most simply stated, is to maximize the sensitivity of the test and its capability of detecting irreversible molecular events leading to neoplastic transformations of cells which could also occur as the result of low level exposure [*40*, p. 127].

This method is valid as well as practical and necessary because

> The intrinsic carcinogenicity of a chemical does not depend on dose level although the proportion of animals developing cancers and the earliest time that tumors are detected are usually related to dosage [*48*, p. 131].

Therefore, were environmental levels considerably lower than animal dose levels, this would not invalidate the results of the testing for purposes of human risk assessment. However, in the case of formaldehyde, OTS staff (*7*), the Mount Sinai committee (*15*), and the NTP panel (*14*) have all pointed out that the tumors have occurred in rats at levels comparable to those encountered by humans.

b) Results in laboratory animals are qualitatively relevant to humans since the overall patterns of metabolism are generally similar, although the type and site of cancer induced may differ.

> Basic biological processes of those molecular, cellular, tissue and organ functions that control life are strikingly similar from one mammalian species to another [*50*, p. 85].
>
> . . . [M]etabolic studies have shown that most differences between humans and experimental animals are quantitative rather than qualitative and support the idea that animal results can be used to predict human responses [*1*, p. 126].

For example, the large body of information on the metabolism of benzo[*a*]pyrene shows that the overall pattern of metabolism in all species and systems tested is the same (although the carcinogenic potency may differ) (*53*). It should be noted that several scientific panels have raised the possibility that humans may, in fact, be more vulnerable to certain carcinogenic substances than laboratory animals (*39, 50, 51*). Weighing the usefulness of metabolic studies in human risk assessment, OSHA concluded:

> [I]n general, for the purposes of negating the identification or classification of potential occupational carcinogens, information on metabolism and pharmacokinetics is of extremely little practical value at the present time [*42*, p. 5158].

There is also scientific consensus that a negative human effect cannot be concluded from evidence that the target of the carcinogen differs in humans from that in experimental animals. In experimental carcinogenesis, the type and site of cancer seen may or may not be the same as that recorded in human studies. For example, 2-naphthylamine induces bladder cancer in man, monkeys, dogs, and hamsters but hepatic cancer in the rat (*43*).

> Present knowledge indicates that . . . the responsive target tissues or organs and the types of tumors induced in different species may vary greatly. Therefore . . . the finding of negative results in some other species generally does not detract from the validity of a positive result as evidence of carcinogenicity for the test substance [*38*, p. 39866].

Specifically, as regards formaldehyde, the CPSC states:

> There is no evidence of biological differences between the laboratory animals tested and humans that would decrease the potential for humans to develop cancer when exposed to formaldehyde [*35*].

This is in agreement with the findings of the OTS staff and the NTP panel, that formaldehyde metabolism and its reaction with cellular components is qualitatively the same in all mammalian species examined to date, including man (*7, 14*). The reports also concurred that, although formaldehyde caused nasal cancer in rats, this may not necessarily be the site affected in human beings.

2) It is not now possible to extrapolate from animal data a "safe" population threshold for any carcinogen regardless of the mechanism of action.

> [The] position that there is no presently acceptable way to reliably determine a threshold for a carcinogen for any given population is amply supported by the evidence presented and also represents, to a large extent, a consensus of scientific opinion [*42*, p. 5137].
>
> Methods do not now exist for determining a safe threshold level of exposure to carcinogens. The major obstacle to determining whether there are safe threshold exposure levels for carcinogens is the lack of data on the effects of low exposure levels. . . . Because there is not definitive evidence of the existence of thresholds and because not all cancer variables have been identified, prudence requires that no safe level thresholds be assumed to exist. . . . Exposure to any amount of a carcinogen, however small, must be regarded as an addition to the total carcinogenic risk [*48*, pp. 133–134].
>
> The self replicating nature of cancer, the multiplicity of causative factors to which indi-

viduals can be exposed, the additive and possible synergistic combination of effects, and the wide range of individual susceptibilities work together in making it currently unreliable to predict a threshold below which human population exposure to a carcinogen has no effect on cancer risk [*38*, p. 39876].

. . . [I]t is generally accepted that a population threshold which would define a "risk-free" dose for a group of people composed of diverse individuals, if it exists, cannot now be demonstrated [*1*, p. 12].

This principle applies to any agent that contributes to the carcinogenic process:

[I]t would not be practicable or justifiable to establish different criteria for the identification, classification, or regulation of initiating and promoting agents. OSHA agrees with the NCAB Subcommittee that "any factor or combination of factors which increases the risk of cancer in humans is of concern regardless of the mechanism of action" [*42*, p. 5152].

The mechanisms by which individual carcinogens induce tumors are not easily understood. Even where it may be possible to definitively classify a substance or agent as an initiator, promoter, or complete carcinogen, these distinctions are not practically useful for purposes of regulation. This is because of the impossibility of identifying "population" thresholds for any carcinogen regardless of the mechanism by which it operates. Under defined experimental conditions, a given substance may appear to show a threshold level (that is, a dose level below which it does not increase tumor incidence). However, as indicated by a large-scale bioassay in which a threshold could not be identified for acetylaminofluorine (*54*), such observed thresholds may simply reflect the limited ability of the test system to detect effects at low dose levels. Even where experimental thresholds could be established with certainty, it would be impossible with current information and methods reliably to predict from experimental data the threshold level in humans (*55*). Such predictions are precluded by the difficulty of obtaining quantitative data at very low dose levels in small numbers of animals, variations in human host responses, and possible additive or synergistic effects of other agents that individuals might be exposed to. Thus, regulatory agencies have sought to reduce human exposure to carcinogenic substances to the lowest possible level consistent with relevant social and economic considerations.

From the above discussion it is clearly not necessary that the mechanism of action be definitively established before formaldehyde is identified as a carcinogen. However, the Formaldehyde Institute (*26*) contends that formaldehyde is likely to act primarily via an epigenetic mechanism—causing tumors only at high doses through its cytotoxic or irritant action—and is therefore probably a "threshold" carcinogen. This view is also implied in the Todhunter memorandum (*6*). The epigenetic mechanisms suggested include (i) cell destruction and rapid cell proliferation triggered at high dose levels that prevent DNA repair and detoxification systems from operating effectively and (ii) induction of ulceration, irreversible hyperplasia, or metaplasia only at high dose levels which are premalignant in themselves or serve to promote tumor formation (*6, 26*).

The OTS, the NTP panel, and CPSC staff have rejected this interpretation, citing the substantial body of evidence that shows formaldehyde to be genotoxic and the absence of factual support for the epigenetic or "threshold" theory (*7, 14, 56*). While the promoting effect of formaldehyde may play a part in its overall carcinogenicity, formaldehyde is a potent alkylating agent (*57*); is a mutagen in a wide variety of test systems including microbial, insect, and mammalian systems (*8*); induces sister chromatid exchange in human lymphocytes (*58*); and causes unscheduled DNA repair in HeLa cells (*59*). Formaldehyde is able both to transform mammalian cells in culture at low concentrations and to initiate cell transformation in vitro (*60, 61*). Formaldehyde also enhances the genotoxic effect of peroxides and radiation (*14*). Thus, with regard to the hypothesis that the "carcinogenic effects of formaldehyde are indirect, termed epigenetic," OTS concluded, "There is . . . absolutely no scientific evidence for this hypothesis in the published literature" (*7*, p. A-6).

The NTP panel further noted that "a number of agents were reported to induce epithelial hyperplasia in several types of tissues but they had no carcinogenic or tumor promoting activity associated with them" (*14*, p. 34). The panel "found no evidence that the induction of irritation or, more specifically, of epithelial hyperplasia is a sufficient condition for the carcinogenic activity of an agent" (*14*, p. 34). The NYU studies (*17*) support the NTP panel on this point. If severe irritation and resultant rapid cell turnover were either a sufficient condition or a necessary prerequisite for carcinogenicity of formaldehyde, one would expect an increased effect in animals exposed to a combination of formaldehyde and a strong irritant. However, in the NYU study HCHO and HCl were administered singly and in combination: there was no increased response to the combination of agents although HCl is a gaseous irritant; nor did HCl alone cause tumors although it did induce hyperplasia (*16, 62*).

Scientists from the CPSC responded to the Todhunter memorandum, citing evidence against the "threshold" theories above and rejecting the assertion that the observation of endogenous levels of formaldehyde in animals without spontaneous tumors indicated a threshold (*63*). They reaffirmed their prior conclusion that "there is no evidence demonstrating that there is a threshold for formaldehyde, or a dose level below which it is certain that formaldehyde will not cause cancer" (*35*).

3) Positive human data are not necessary to regard an agent as a likely human carcinogen warranting protective action.

Although epidemiological evidence is a necessary prerequisite to actually calling a substance a "human carcinogen," this is a point of terminology rather than a criterion for taking protective action. The most powerful reason is that the usefulness of epidemiology for the identification of carcinogens is limited by a number of constraints. These include cost, the usual long lag between exposure and appearance of cancer, the confounding effect of multiple exposures to carcinogens, and difficulties in identifying an appropriate control group [see (*48*, pp. 125–128)]. A practical problem is that very large samples must be compared if the risk in the unexposed population is low and the number expected to show the effect is small. Because of the possibility of a false negative result, the absence of positive results cannot prove an absence of risk; however, an absence of positive results may be useful in placing upper bounds on the magnitude of the risk (*64*):

. . . [N]egative epidemiological data, questionable because of limitations in the power of detection of such studies, do not deny the conclusion of carcinogenicity on the basis of animal assays [*38*, p. 39871].

Thus:

When a toxic substance is identified in a mammalian test system (in which the criteria listed in the standards are used) as a prudent health policy matter this substance is to be treated as posing a carcinogenic risk to human beings. . . . Because public policy mandates preventive health care, waiting for epidemiologic data is unacceptable, since it means waiting to "count dead bodies" [*41*, pp. 14–16].

Specifically, as regards formaldehyde: epidemiological studies completed to date have not been specifically designed to evaluate the carcinogenicity of formaldehyde in human populations; thus they

have been inconclusive or suggestive of a positive effect rather than negative regarding the carcinogenicity of formaldehyde.

These studies are inconclusive, because of small study size (the three studies together cover fewer than 2,000 deaths), poor documentation of exposure, possible multiple exposures, and study design limitations [7, p. 17].

Epidemiological studies conducted to date do not permit a definitive evaluation of the carcinogenic risk of formaldehyde to humans [9, p. 4].

Citing the conclusions of the NTP panel, CPSC stated:

The epidemiological studies presented at the CIIT conference and by the Formaldehyde Institute do not have sufficient information to be considered conclusive because of the small population size, lack of exposure data, and other confounding factors [35, p. 88].

As IARC has noted, three proportional mortality studies of workers exposed to formaldehyde had only very limited (7 to 12 percent) power to detect a threefold excess of mortality from nasal cancer (27). However, a number of studies have been suggestive of an increased cancer risk (19, 36, 65).

The preliminary epidemiological findings suggest that persons occupationally exposed to formaldehyde may experience elevated risks for certain cancers, notably of the pharynx, oral cavity, lymphatic and hematopoietic system, brain and skin [65, p. 8].

Recently, there have been several reports of rare nasal tumors in workers exposed to formaldehyde (66, 67).

According to the OTS, "because of inherent limitations, studies in progress are not likely to resolve present concerns about formaldehyde safety" (7, p. 17). This is true of an ongoing NCI study that will not be completed for at least 2 years (68). "Analysis of the design of the study . . . suggests that it may not be powerful enough to assure that formaldehyde is not carcinogenic in humans" (7, p. 27).

In summary, the IARC has evaluated the laboratory and epidemiological data on formaldehyde gas and has stated: "There is sufficient evidence that formaldehyde gas is carcinogenic to rats. Epidemiologic studies provide inadequate evidence to assess the carcinogenicity of formaldehyde to man." In accordance with its established policy (52) therefore, the working group concluded that in the absence of adequate epidemiological data, formaldehyde gas should be considered, for practical purposes, as if it represented a carcinogenic risk to man (27, p. 50).

Conclusion

Over several decades, the results of scientific research have led to policies for assessing carcinogens that have been widely endorsed by the scientific community and accepted by regulatory agencies in this country and abroad. These policies are based on the principles that valid positive animal data are presumptive evidence of carcinogenicity in humans and that population thresholds cannot be identified for carcinogenic substances. These two principles are the heart of present federal programs to protect human health from cancer-causing chemicals, and are consistent with accepted social policy that makes a conscious decision to err on the side of caution in addressing health risks. The present behavior of two U.S. regulatory agencies regarding formaldehyde suggests that they are disregarding the substantial evidence and rationale on which the established policies relating to assessment and regulation of carcinogens have been based. Indeed, it appears that EPA is informally revising its cancer policy to decrease reliance on animal studies—a step that could have the effect of substantially delaying or indeed barring altogether protective action on substances such as formaldehyde, pending the development of positive epidemiological data.

References and Notes

1. Office of Technology Assessment, *Assessment of Technologies for Determining Cancer Risks from the Environment* (OTA, Washington, D.C., June 1981).
2. H. H. Hiatt, J. D. Watson, J. A. Winsten, Eds., *The Origins of Human Cancer* (Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1977).
3. M. Sun, *Science* **214**, 525 (1981).
4. *Inside EPA* (16 October 1981), p. 12.
5. R. J. Smith, *Science* **212**, 1482 (1981).
6. J. Todhunter, "Review of data available to the Administrator concerning formaldehyde and di-(2-ethylhexyl)phthalate (DEHP)," memorandom to A. M. Gorsuch, 10 February 1982.
7. Environmental Protection Agency, Office of Toxic Substances, *Options Paper on Formaldehyde* (Office of Toxic Substances, Washington, D.C., 11 September 1981).
8. National Academy of Sciences, *Formaldehyde and Other Aldehydes* (National Academy of Sciences, Washington, D.C., 1981).
9. National Institute for Occupational Safety and Health, *Current Intelligence Bulletin No. 34* (15 April 1981).
10. K. C. Gupka, A. G. Ulsamer, P. Preuss, paper presented at the International Symposium on Indoor Air Pollution and Energy Conservation, Amherst, Mass., 13 to 16 October 1981.
11. This standard can be compared to threshold limit values (TLV's) for Sweden, Norway and Denmark of 1 ppm and for the U.S.S.R. of 0.4 ppm. In West Germany formaldehyde is listed as an occupational carcinogen (K. Hemminki, Institute for Occupational Health, Finland, personal communication, January 1982).
12. J. A. Swenberg, W. D. Kerns, R. I. Mitchell, E. G. Gralla, K. L. Pavkov, *Cancer Res.* **40**, 3398 (1980).
13. Chemical Industry Institute of Toxicology, *Final Report on a Chronic Inhalation Toxicology Study in Rats and Mice Exposed to Formaldehyde* (Battelle Columbus Laboratories, Columbus, Ohio, 1981). Data released to the International Agency for Research on Cancer (IARC) Working Group, Research Triangle Park, N.C., 19 October 1981.
14. R. A. Griesemer, chairman, *Report of the Federal Panel on Formaldehyde* (National Toxicology Program, Research Triangle Park, N.C., November 1980).
15. I. J. Selikoff *et al.*, *Carcinogenicity of Formaldehyde: Final Report* (Report to the American Cancer Society, 25 February 1981).
16. R. E. Albert, A. R. Sallakumar, S. Laskin, M. Kuschner, N. Nelson, C. A. Snyder, *J. Natl. Cancer Inst.* **68**, 597 (1982).
17. A. Upton, letter to V. de Vita *et al.*, 17 August 1981.
18. Chemical Industry Institute of Toxicology, *Statement Concerning Research Findings, Docket No. 11109* (CIIT, Research Triangle Park, N.C., 8 October 1979).
19. Environmental Protection Agency, *Priority Review Level 1: Formaldehyde* (Office of Toxic Substances, 19 February 1981).
20. That section provides that when the Administrator receives information indicating that a chemical may pose a significant risk of cancer, birth defects, or gene mutations, EPA must initiate appropriate regulatory action or publish a finding that the risk is not unreasonable within 180 days.
21. Memorandum from Chairman Moffett to members of the subcommittee on environment, energy, and natural resources, 6 October 1981.
22. The House of Representatives subcommittee on environment, energy, and natural resources of the Committee on Government Operations, Hearing, 21 October 1981; "Environment aides industry talks criticized," *New York Times* (22 October 1981).
23. *Inside EPA* (25 September 1980), pp. 4–5.
24. M. Cowan, memorandum to Secretary of OSHA Thorne Auchter, *Health Safety Lett.* (22 July 1981).
25. H. Young, United Auto Workers Petition for Emergency Temporary Standard on Formaldehyde, sent to T. Auchter, 26 October 1981.
26. J. Bender, letter to T. Auchter, 28 August 1981. The views of the Formaldehyde Institute are also expressed in S. J. Byington, Formaldehyde Institute, memorandum to J. C. Miller, Task Force on Regulatory Relief, 23 February 1981; H. Demopoulos, testimony before the Department of Energy, 20 February 1981; H. Demopoulos, J. Cimino, B. Wagner, "An academic review of the possible adverse health effects of formaldehyde," paper presented to the CPSC, 20 March 1981; and J. Ramey, chairman of the Formaldehyde Institute, letter to J. Hernandez, EPA, 31 August 1981.
27. Report of the IARC Working Group on the Evaluation of Carcinogenic Risks of Chemicals to Humans, *IARC Monogr.*, in press.
28. A. Upton and I. B. Weinstein, letter to T. Auchter, A. M. Gorsuch, and N. H. Steorts (29 January 1982).
29. Statement adopted by the Board of Directors, American Cancer Society, New York City, 5 February 1982.
30. "Product safety agency bans use of formaldehyde foam insulation," *New York Times* (23 February 1982), p. 15.
31. M. Sun, *Science* **213**, 1232 (1981). The Massachusetts ban has been set aside by the Superior Court; that decision is on appeal.
32. Report of the Pathology Group Review of the CIIT Studies on Formaldehyde Exposure in Rodents (Chemical Industry Institute of Toxicology, Research Triangle Park, N.C., February 1980); E. G. Gralla, H. d'A. Heck, L. W. Hrubesh, G. W. Meadows, *A Report of the Review of the Formaldehyde Exposure* (Chemical Industry Institute of Toxicology, CIIT Docket No. 62620, Research Triangle Park, N.C., 14 January 1980).
33. *Proceedings of the CIIT Conference on Formaldehyde Toxicity* (Hemisphere Publishing, New York, in press).
34. R. E. Albert, personal communication, September 1981.
35. Consumer Product Safety Commission, "Urea-formaldehyde foam insulation proposed ban: denial of petition," *Fed. Regist.* **46**, 11188 (5 February 1981).
36. P. F. Infante, A. G. Ulsamer, D. Groth, K. C. Chu, J. Ward, *Lancet* **1981-II**, 980 (1981).
37. National Cancer Advisory Board, *J. Natl. Cancer Inst.* **58**, 461 (1977).
38. Interagency Regulatory Liaison Group, *Fed. Regist.* **44**, 39858 (6 July 1979).
39. National Research Council, *Summary Report: Drinking Water and Health* (National Research Council, Washington, D.C., 1977).
40. Food Safety Council, *Proposed System for*

Food Safety Assessment (Food Safety Council, Washington, D.C., June 1980).
41. R. Ruttenberg and E. Bingham, *Ann. N.Y. Acad. Sci.* **365**, 13 (1981).
42. Occupational Safety and Health Administration, *Fed. Regist.* **45**, 5002 (25 January 1980).
43. International Agency for Research on Cancer, *IARC Monogr.* **15**, 11 (1977).
44. E. C. Hammond and I. J. Selikoff, Eds., *Ann. N.Y. Acad. Sci.* **329** (1979), entire volume.
45. W. Nicholson, Ed., *ibid.* **363** (1981), entire volume.
46. Environmental Protection Agency, *Fed. Regist.* **41**, 24102 (25 May 1976).
47. _____, *ibid.* **44**, 58642 (10 October 1979). See pp. 58647 and 58656.
48. Toxic Substances Strategy Committee, *Toxic Chemicals and Public Protection* (TSSC, Washington, D.C., May 1980).
49. International Agency for Research on Cancer, *IARC Monogr. Suppl. No. 1* (1979).
50. D. P. Rall, *Ann. N.Y. Acad. Sci.* **329**, 85 (1979).
51. _____, in *IARC Sci. Publ. No. 25* (1979).
52. International Agency for Research on Cancer, *IARC Monogr.* **20**, 7 (1979).
53. P. Brookes and M. E. Duncan, *Nature (London)* **234**, 40 (1971); P. Sims, in *Chemical Carcinogenesis Essays*, R. Montesano, L. Tomatis, M. David, Eds. (IARC, Lyon, France, 1974), p. 57; H. V. Gelboin and P. O. P. Ts'o, Eds., *Polycyclic Hydrocarbons and Cancer* (Academic Press, New York, 1978).
54. N. A. Littlefield, J. H. Farmer, D. W. Gaylor, W. G. Sheldon, *J. Environ. Pathol. Toxicol.* **3**, 17 (1979).
55. This statement is based on the passages quoted above and on conversations with F. Burns, NYU; I. B. Weinstein, Columbia University; and T. Slaga, Oak Ridge National Laboratory.
56. R. L. Medford, *Decision-Briefing Package on Urea-Formaldehyde Foam Insulation* (Consumer Product Safety Commission, Washington, D.C., February 1982).
57. R. J. Wilkins and H. D. Macleod, *Mutat. Res.* **36**, 11 (1976); N. Magana-Schwenke and B. Ekert, *ibid.* **51**, 11 (1978).
58. G. Obe and B. Beck, *Drug Alc. Depend.* **4**, 91 (1979).
59. C. N. Martin, A. C. McDermid, R. C. Garner, *Cancer Res.* **38**, 2621 (1978).
60. D. J. Brusick, B. C. Myhr, D. G. Stetka, J. O. Rundell, *Genetic and Transforming Activity of Formaldehyde* (Litton Bionetics Report, Litton Bionetics, Kensington, Md., April 1980).
61. D. L. Ragan and C. J. Boreiko, *Cancer Lett.* **13**, 325 (1981).
62. R. E. Albert, personal communication, November 1981.
63. K. Gupta and M. Cohn, *Health Sciences Analysis of Comments on the Proposed Ban of UFFI* (Consumer Product Safety Commission, Washington, D.C., 19 February 1982).
64. C. S. Muir, *Ann. N.Y. Acad. Sci.* **329**, 153 (1979).
65. A. Blair, *Formaldehyde*, presentation to the National Cancer Advisory Board (5 October 1981).
66. P. Infante, "Documentation of excess nasal cancer among workers exposed to formaldehyde," memorandum to the Consumer Product Safety Commission, 19 January 1982.
67. W. E. Halperin, M. Goodman, L. Staynor, L. J. Elliott, R. A. Keenlyside, P. J. Landrigan, in preparation.
68. According to A. Blair, National Cancer Institute, the study will not be completed earlier than summer 1984 (personal communication, December 1981).

Food Science and Nutrition: The Gulf Between Rich and Poor

Joseph H. Hulse

Summary. The people of economically developed countries benefit greatly from modern food science. They are protected from food contamination, have access to a great variety of food, and need spend little time preparing it. The poor in developing countries enjoy few of the benefits of food science. Their diets are often nutritionally deficient and they spend many hours each day processing their food and searching for wood with which to cook it. In most tropical countries food losses between harvest or slaughter and eventual consumption are inestimable. Efforts to improve post-harvest food systems in developing countries require the attention and ingenuity of many scientific disciplines and the support of all development agencies.

The Brandt Commission (*1*) describes the gap which separates rich and poor nations as being so wide that at the extremes people seem to live in different worlds. The contrast in life-styles is particularly evident in the relative quality of their diets, to which food science has contributed so much for the richer and so little for the poorer.

Food Science in Developed Countries

Historically, food science has been devoted to an understanding of the biochemical and biophysical nature and composition of foods, the changes that foods undergo after harvesting, and during such traditional technological transformations as fermentation, milling, drying, frying, baking, boiling, and other forms of cooking. For people in developed countries, food science combines the skills and knowledge of chemists, physicists, microbiologists, nutritional biochemists, engineers, and many other professions to provide the most varied range of wholesome diets in the history of mankind. From large grocery stores people can choose several thousand different food items at all times of the year, and many spend less than a quarter of their disposable income on feeding themselves. As much as, if not more, than any other branch of learning, food science has made it possible for both parents in a household to pursue their careers without detriment to the adequacy or variety of their family's diet.

The raw materials of the food scientist are more highly and uncontrollably variable than most of those used by inorganic chemists. The properties and composition of the seeds and fruits of cultivated plants are influenced by genetic background, the environmental conditions of soil and climate under which they are grown, and the methods by which they are harvested, stored, and processed. At all stages after harvesting, both during and after processing, changes take place involving so many diverse and complex chemical reactions that it is impossible to follow any one in isolation from the rest. Consequently, the extensive body of knowledge acquired has resulted from both biochemical and biophysical measurement and from empirical observation.

Many food plants, including those widely accepted, contain substances unsuitable for ingestion. Some, for example, contain mycotoxins resulting from infection of grains in the natural environment; others synthesize toxic substances that protect them. Primitive people, probably by trial and error, found simple ways to eliminate, or reduce to relatively safe levels, naturally occurring toxins and nutritional inhibitors present in their staple food sources. Typical are the

Joseph H. Hulse is Director, Agriculture, Food and Nutrition Sciences, International Development Research Centre, Ottawa, Canada K1G 3H9. This article was prepared on behalf of the organizing committee of the forthcoming IUPAC/IRRI-CHEMRAWN II International Conference on "Chemistry and World Food Supplies—The New Frontiers" to be held in Manila, Philippines, 6 to 10 December 1982.

0036-8075/82/0618-1291$01.00/0