COMMENTARY

Evolving Concepts of Chemical Sensitivity

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Chemical sensitivity appears to be an elusive phenomenon. Studies on individual differences in susceptibility may provide glimpses into the range of sensitivity in a population, which can be used for further study. Preliminary evidence in laboratory animals suggests the range of sensitivity to manufactured chemicals may span orders of magnitude. Determining the reasons that underlie individual differences in sensitivity is a more difficult enterprise. Conditioning of adverse physiological effects of airborne chemicals may play a vital role in the etiology of chemical sensitivity, and it provides a rigorous laboratory model by which to investigate some aspects of this elusive phenomenon. — Environ Health Perspect 105(Suppl 2):455–456 (1997)

Key words: chemical sensitivity, susceptibility, conditioning

Introduction

The purposes of the workshop at which this report was presented were to gain insights into chemical sensitivity and to suggest approaches for testing notions regarding the etiology of chemical sensitivity. While much has been written recently about the topic, multiple chemical sensitivity remains an elusive phenomenon. Nevertheless, and perhaps together with the equally elusive phenomena of sick-building and Persian-Gulf syndrome, multiple chemical sensitivity raises basic questions regarding the range of sensitivity in the population to environmental chemicals, and the conditions that differentiate individuals at the extremes. Variation in sensitivity has rarely been the focus of research because scientists generally have been preoccupied with measures of central tendency. Moreover, when error estimates (typically standard errors) are attached to dose–effect curves, these are considerably smaller than the range of observations in the data. Recent evidence suggests, however, that the range of individual differences, even in laboratory research, may be great. For example, using a novel probabilistic dose-tolerance analysis (*1*), researchers estimated that the range ($\bar{x} \pm 3$ SD) of doses of pesticides and solvents producing small deficits in neurobehavioral function in adult male, healthy outbred rats and mice was 1.5 to 4 orders of magnitude (*2*). How much greater the range would be after including gender, different ages, and a compromised physiology is unknown. These findings suggest that the traditional use of an uncertainty factor of 10 in calculating reference doses (RfDs) and reference concentrations (RfCs) to compensate for individual differences in sensitivity may be woefully inadequate.

Regarding the development of chemical sensitivity, two popular scenarios involve "big-bang" and "kindling" events. The former refers to an acute overexposure to a toxicant that leads to chemical sensitivity. There is some support for this scenario as certain chemically sensitive individuals report an initiating event, often one that involves exposure to a pesticide. Kindling refers figuratively to repeated low-level exposure to a toxicant that ultimately results in clinical symptomatology. The term kindling is taken from a well-defined area of research in which daily low-level electrical stimulation of certain brain regions ultimately produces seizures in laboratory rats (*3*). Seizures are not, however, reported in chemical sensitivity, so use of the term should not imply a mechanism for inducing chemical sensitivity. Nevertheless, Miller (*4*) has tried in her model to integrate these two scenarios; an initiating event, followed by low-level, repeated exposure leads to chemical sensitivity. For reasons outlined below, the big-bang notion is plausible and testable, while the kindling notion has inherent difficulties in accounting for the etiology of chemical sensitivity.

It seems likely that pesticide overexposure may serve as an initiating event. Researchers should avoid speaking in generalities, however, since the number of pesticides, along with their effects and mechanisms of action, is legion. It further appears that organophosphate pesticides may be likely causal agents. This seems plausible because many organophosphates are aromatic thiol-containing compounds. Furthermore, acute overexposure to organophosphates has been reported to produce many flulike signs and symptoms that are reported by chemically sensitive individuals. It is possible that the subsequent odor of the organophosphate may reinstate signs and symptoms of overexposure through the well-established mechanism of classical conditioning (*5*). Given the recent interest in human organophosphate neurotoxicity (*6,7*), it would be interesting to include evaluations of odor aversions and chemical sensitivity in future research in this area.

Miller (*4*) introduced the concept of toxin-induced loss of tolerance (TILT). The choice of words is unfortunate for two reasons. First, toxicologists draw a distinction between toxins, which are naturally occurring, and toxicants, which are synthetic chemicals. Most of Miller's presentation has dealt with toxicants. Second, tolerance is precisely defined in the drug abuse research literature. The acute effect of a drug diminishes over time with repeated (usually daily) treatment. Larger doses are then needed to produce the initial effect, leading to a rightward shift in the dose–effect function on redetermination. Following cessation of treatment, tolerance is gradually lost and the dose–effect function reverts toward its original location (*8*). Use of the words toxin and tolerance in describing the etiology of chemical sensitivity will likely create confusion in an already confused area of inquiry that could hamper laboratory and clinical research into this phenomenon.

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Abbreviations used: RfCs, reference concentrations; RfDs, reference doses.

N. Cohen (*9*) has presented a wealth of research findings in the area of psychoneuroimmunology. Using an elegantly simple classical conditioning paradigm involving flavored solutions, called flavor-aversion conditioning (*10*), Cohen has demonstrated impressive alterations in immune function and in the survivability of immunocompromised rats. Elaborate use of many control conditions leads to the conclusion that conditioning can profoundly alter immune function in laboratory rats. There is now a wealth of data on the modification by conditioning of many other basic physiological processes, including cardiovascular function, respiratory function, and gut motility (*10*). Flavors and odors appear to be prepotent stimuli in forming these types of conditioned associations. Application of these types of behavioral conditioning preparations would be beneficial in attempts to understand the etiology of chemical sensitivity, especially in light of the plausibility of the big-bang scenario mentioned above.

Finally, Cohen's work, along with that of many others makes it clear that the mind–body distinction is bogus and should have been laid to rest 40 or 50 years ago. The ability to form conditioned associations is every bit an integral part of the biological make-up of an organism as are processes like gustation and gestation. Attempts at demarcating chemical sensitivity into purely mental or organic phenomena will be futile and will undermine the extensive interdisciplinary collaborations that are needed to fully understand the dimensions and dynamics of the phenomenon.

REFERENCES

1. Glowa JR, MacPhail RC. Quantitative approaches to risk assessment in neurotoxicology. In: Neurotoxicology: Approaches and Methods (Chang L, Slikker W Jr, eds). New York:Marcel Dekker, 1995;777–787.
2. MacPhail RC, Glowa JR. An animal model for assessing individual differences in susceptibility to environmental pollutants. Presented at the Annual Meeting of the Society of Risk Analysis, December 1996, New Orleans, Louisiana.
3. Gilbert ME. Neurotoxicants and limbic kindling. In: The Vulnerable Brain and Environmental Risks, Vol 1 (Isaacson RL, Jensen KF, eds). New York:Plenum Press, 1992;173–192.
4. Miller CS. Toxicant-induced loss of tolerance: an emerging theory of disease? Environ Health Perspect 105(Suppl 2):445–453 (1997).
5. Siegel S, Kreutzer R. Working Group Report 2: Pavlovian conditioning and MCS. Environ Health Perspect 105(Suppl 2):521–526 (1997).
6. Savage E, Keefe TJ, Mounce LM, Heaton RK, Lewis JA, Burcar PJ. Chronic neurologic sequelae of acute organophosphate pesticide poisoning. Arch Environ Health 43:38–45 (1988).
7. Steenland, K, Jenkins B, Ames RG, O'Malley M, Chrislip D, Russo J. Chronic neurologic sequelae to organophosphate poisoning. Am J Publ Health 84:731–736 (1994).
8. MacPhail RC, Seiden LS. Effects of intermittent and repeated administration of *d*-amphetamine on restricted water intake in rats. J Pharmacol Exp Ther 197:303–310 (1976).
9. Cohen N, Kehrl H, Berglund B, O'Leary A, Ross G, Seltzer J, Weisel C. Working Group Report 3: Psychoneuroimmunology. Environ Health Perspect 105(Suppl 2):527–529 (1997).
10. MacPhail RC, Peele DB. Animal models for assessing the neurobehavioral impact of airborne pollutants. Ann NY Acad Sci 641:294–303 (1992).