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Commentary

Expanded Operational Concept of High Risk Groups and Its Role in Standard Setting

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The role of the knowledge of high risk groups in the standard-setting process is examined. The overall conclusion is that many potential high risk segments of the population have not been studied adequately and that this deficiency in our knowledge markedly reduces the ability of decision makers to derive appropriate regulatory decisions by either ignoring the potential health effects or applying potentially excessive and expensive safety factors.

Introduction

The need to consider high risk groups in the standard-setting process has been a principal concern to the regulatory and medical community. It is obvious that if the high risk segments of the community can be protected then the entire population will also be assured safety. However, the issue is where to draw the line. Is it possible to protect the entire population adequately? What information do regulatory officials require when they have to decide on whether a specific type of high risk group should be protected by ambient standards? A critical regulatory issue in environmental health today, therefore, is what to do with high risk groups.

High Risk Groups

The first step in this process is the acquisition of knowledge as to the groups in the population who are at increased risk. Without such knowledge informed regulatory decisions cannot be made.

Individuals may be at increased risk to pollutant toxicity as a result of several biological factors including developmental/aging processes, genetic factors, nutritional status, pre-existing diseases and lifestyle/personal habits. Numerous examples of each of these categories have been identified (*1*). For example, nearly 30 genetic conditions exist which may enhance one's susceptibility to environmental toxicants while a recent book has documented how nutritional status alters one's susceptibility to pollutant-induced adverse health effects (*2*).

Despite the growing awareness of the existence of differential susceptibility to pollutant toxicity within the population and the potential significance of this type of knowledge in the standard-setting process, the field of high risk group identification, validation, and quantification is essentially in its developmental infancy despite its quasiregulatory origin numerous years ago by the American Conference of Governmental Industrial Hygienists (*3*). The relative newness of much of this field creates problems for the standard-setting process, since national ambient air and drinking water standards have frequently been established without a comprehensive assessment of the effects on potential high risk groups (*3*), even though the primary ambient air standards recognized that children, the aged and individuals with various respiratory/immunological diseases were the first to experience distress upon exposure to sufficient levels of gaseous and particulate irritants and that persons with coronary heart disease were at enhanced risk to carbon monoxide intoxication. However, as implied above, the high risk group concept is much broader than is frequently perceived even by those in the field. For example, while it is known that persons with any of the following hereditary red blood cell disorders such as acatalasemia, glucose-6-phosphate dehydrogenase deficiency

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(G-6-PD), thalassemia, and methemoglobin reductase deficiency are at increased risk to certain oxidant stressor agents (*1*), whether and to what extent persons with such genetic conditions are at increased risk to environmental oxidants such as ozone or nitrogen dioxide is essentially unknown. In addition, *in vitro* studies have recently shown that humans with altered hemoglobin (i.e., hemoglobin M) have a markedly greater affinity for carbon monoxide than those with normal hemoglobin (*4*). Differential affinity of carbon monoxide for different human hemoglobin variants has never been considered in the standard-setting process because of a lack of sufficient data but such knowledge could have important biomedical implications. Furthermore, while current standards have addressed some groups at increased risk to respiratory irritants, several potential high risk groups to these pollutants (*1*), such as those with serum$_1$ antitrypsin deficiency and its carrier state; immunologulin A deficiency, carriers of cystic fibrosis and those with inadequate levels of vitamin E, remain to be more fully assessed. With the prominent exceptions mentioned above and the recognized enhanced developmental susceptibility of the very young to lead and nitrate (*3*), inclusion of high risk group knowledge in the process of setting national ambient standards has been for all intents and purposes absent.

The lack of inclusion of high risk group knowledge in the standard-setting process does not appear to be due to a lack of concern by regulatory officials but to a lack of quantitative dose-response relationships describing the magnitude of the increased susceptibility of potential high risk assessments. It is clear that conditions resulting in enhanced risk in the population exist and may be quite numerous in certain situations (e.g., 11% of the American black male population have an erythrocyte G-6-PD deficiency, 4% of the Caucasian population are carriers of cystic fibrosis, 1% of the American population are thought to display an intermediate ability to repair damaged DNA and are at significantly greater risk of developing cancer) (*5*).

Despite the dearth of data on the effects of ubiquitous air pollutants such as carbon monoxide, nitrogen dioxide, and ozone on many but not all potential human high risk groups, there is a dangerous and false notion growing that these pollutants have been studied sufficiently and there is little or nothing to be gained in a regulatory sense from further research in these areas. To make such a statement totally overlooks the biochemical basis for the potential enhanced susceptibility of other subgroups within the population.

Animal Models of High Risk Groups

Several major problems exist in attempting to acquire knowledge of pollutants on high risk groups. First, finding and/or developing a sufficiently predictive animal model is one approach. Since there are animals with a red cell catalase deficiency, i.e., certain laboratory strains of mice (*6*) and presumably all dogs (*7*), and erythrocyte G-6-PD deficiency, e.g., several strains of sheep (*8*), sickle cells, i.e., deer (*9*), genet (*10*), sheep (*11*), and thalassemia (i.e., the Bulgarian rat (*12*), the possibility exists that immediately useful data could be provided to decision makers from toxicological studies with such models. However, critical assessments of these respective models finds each one lacking in their respective predictive potential. For instance, all of the known causes of sickling in animal models occur after oxygenation and increased pH of the blood, while human erythrocyte sickling takes place with the totally opposite stimulus (*9-11*). The G-6-PD deficiency of sheep is apparently sufficiently like that of the human A-variant (i.e., the most numerous form). Unfortunately, the red cells of the sheep have major differences in several other enzyme activities which severely reduce the predictive utility of this model. More specifically, sheep have 5.1 times greater erythrocyte glutathione peroxidase activity than humans but only 20% of the normal human values for red cell catalase and glutathione reductase (*13, 14*). In addition, the low G-6-PD activity of sheep is a biochemical characteristic of the respective substrains with there being a lack of a high or "normal" G-6-PD activity in these sheep (*8*). Thus, there is a lack of adequate within strain comparison to evaluate the hypothesis that a G-6-PD deficiency alone enhances ozone toxicity in contrast to the genetic polymorphism of the enzyme in the human population.

The problem here is one of very high expectations from the predictive capabilities of the animal model. The model is required to provide not only qualitative but also quantitative accuracy as well. This is especially difficult to ask for when it is realized that there are at least six different enzymes in the red cell which affect susceptibility to oxidant stress. To find a model which matches adequately over six enzymes may be expecting too much.

Role of Human Studies

The lack of adequate animal models to evaluate the hypothesis that environmental oxidants such as ozone and nitrogen dioxide may pose a greater risk to persons with any of the above-mentioned hereditary disorders does not suggest that the respective hypotheses are not valid but that they require testing in another system, namely with humans. If there is a lack of an appropriate animal model and the policy concern of specific high risk groups is sufficiently high, then the agency must face the ethical issue of testing high risk groups in clinical toxicological settings or considerably more expensively via the implementation of epidemiological methodology. Ignoring the problem because it is controversial is not the answer. If the hypothesis is of high enough social concern, then it must be directly addressed in ways which are morally and medically responsible.

This approach is not necessarily leading to a conclusion that all high risk groups must be protected at all costs. That's a societal decision, a value judgment, and not a scientific issue. The previously articulated arguments are designed to reveal that current ambient air quality standards are based on data which are strikingly incomplete despite years of study. Standards have been in fact established for which there is little knowledge of whether and to what extent they protect sizeable potential human high risk groups. This is not to even suggest that all or even more than a small percentage of sizeable potential high risk groups may prove to actually exhibit a significantly enhanced predisposition to pollutant-induced adverse health effects. However, this knowledge is essential for decision makers regardless of the findings.

New Approaches for Developing Animal Models

The previous statements which challenged the use of present animal models to predict adequately oxidant-induced red cell changes in potential human high risk groups illustrate the need of environmental toxicology to find or develop novel approaches toward utilizing animal models which predict human high risk group responses. Even though current sampling of the common laboratory models has often proved inadequate for the type of predictions required, there is good potential in at least several general areas.

One is to find animal models of human high risk groups via the ecological approach. For example, since humans heterozygous for thalassemia or with a G-6-PD deficiency have a selective advantage in areas of endemic malaria, similar types of adaptations may have occurred in other animals living in the same habitat. In fact, two kinds of malaria, *P. berghei* and *P. vinckei,* are endemic in rodents of the Congo, Nigeria and other parts of Africa. A survey of wild rodents in these areas may reveal animal models that have also adapted to malarial environments by evolving red cell alterations comparable to humans and thereby may provide potential models for toxicological study (*15*).

Since there is a lack of adequate predictive sickle cell animal models, Castro et al. (*16*) decided to create a new model type by placing the human red cells with hemoglobin S in the rat model after its phagocytizing capacity had been knocked out. Initial studies have revealed that it may offer potential to evaluate the responses of human sickle cells in experimental settings since transfused sickle and normal cells maintained the same relative survival times in the rat model as in the human. This model, however, requires considerable development before it may offer any practical possibilities for the regulatory agencies. This transfusion model deserves considerable attention because it offers the potential of being applied to the other common red cell hereditary disorders such as thalassemia and G-6-PD deficiency. This is not meant to diminish the inherent problems resulting from the disruption of the normal function of the reticuloendothelial system and complement via chemical treatment in order to permit the human red cell not to be rapidly rejected upon transfusion.

It may be possible to exploit the differences. When extrapolation of animal studies to humans is required, the issue invariably raised is "which human." Mankind is highly diverse—genetically, culturally and developmentally—with a markedly differential susceptibility to pollutant-induced adverse health effects. No one animal model can predict the responses of such a diverse grouping as man. However, the recognition of the diversity of potential models suggests that from this vast array of animals, different systems could be found to reasonably stimulate selected human high risk groups or normally functioning individuals. Many biochemical parameters such as enzyme activity levels, dermal thickness, repair processes, hemoglobin variants, and others, display such a range and diversity within the animal kingdom that it may be possible to find one or

more which respond similarly as some human subgroup.

Summary

Where to draw the line in terms of setting ambient air/water quality standards is a societal value and not a scientific issue. However, it is up to the research scientists to provide decision makers with as comprehensive as possible an assessment of what biomedical effects each incremental dose of pollutant exposure has on the general population as well as subgroups within the population who may be at increased risk to the pollutant. It is contended that many of these potential high risk segments have not been studied, and this lack of knowledge compromises the ability of decision makers to make appropriate regulatory decisions by either ignoring the potential health effects or applying potentially excessive and expensive safety factors.

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