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Populations at Risk: Addressing Health Effects Due to Complex Mixtures with a Focus on Respiratory Effects

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Some individuals in the population may be sensitive or susceptible be to the effects of air pollutants. Such sensitivity may be to specific pollutants or classes of pollutants. However, sensitivity or susceptibility in some individuals can be to all irritants, but the sensitivity is likely to be response specific or organ specific. The U.S. Clean Air Act specifically recognizes that some individuals in the population are sensitive to air pollutants and indicates that such individuals need to be protected by air quality standards.

It is usually difficult to determine the cause of sensitivity, though various biological mechanisms have been studied. Biological age may be a factor, with the young being most sensitive and susceptible to being affected. An example is the heightened bronchial lability and responsiveness in the very young that appears to disappear with growth. Susceptibility may be innate (e.g., genetic) and/or induced by events/exposures. Frequently, those with preexisting illnesses are part of the sensitive population because they may often respond, sometimes hyperrespond, to a pollutant exposure that may not affect most people. Asthmatics are excellent examples of individuals who were susceptible to the disease and, once inflicted, are susceptible to the effects of many environmental and nonenvironmental agents. Usually only a fraction of the general population will respond with heightened reactions at lower doses. Such individuals require special evaluation and attention in all exposure–response studies and risk assessments. Thus, the conditions defining populations at risk and the methodologies to discover and study them can be reviewed.

Introduction

There are two basic concepts concerning populations at risk. The first relates to the epidemiological definition, which states that such populations are those exposed to the agent(s) of concern. This can be extended to connote those exposed to certain concentrations of a pollutant/contaminant or to certain complex mixtures of pollutants. This concept is critical in risk assessment and policy decisions, as there may be many, or few, populations exposed to given contaminants or to their complex mixtures, or to concentrations of those contaminants above a given guideline or standard. Of course, accurate exposure assessment is essential for determining the population at risk using this definition.

There is a related epidemiological definition, that of populations with given risk factors. Risk factors are, according to the *Dictionary of Epidemiology* (*1*), aspects of environmental exposure, inborn (or inherited) characteristics, and/or personal behavior (or lifestyle), which on the basis of epidemiological evidence fare known to be associated with health-related condition(s) considered important to prevent. (Synonyms of risk factors are "risk markers," "determinants," and "modifiable risk factors.") Those populations with the risk factor(s) are susceptible (or "sensitive") populations.

It is also critical to denote those populations at risk to given contaminants or to stated concentrations of those contaminants because they are "sensitive" populations; this and the definition related to populations with risk factor(s) lead to the second basic concept, that of the sensitive population(s). Thus, some individuals in the population may be sensitive to or susceptible to the effects of pollutants. Such sensitivity may be to specific pollutants or classes of pollutants. However, sensitivity or susceptibility in some individuals can be to all irritants, but sensitivity is likely to be response specific or organ specific. The U.S. Clean Air Act specifically recognizes that some individuals in the population are sensitive to air pollutants and indicates that such individuals need to be protected.

Most individuals will respond to some irritants at some concentration. All studies have shown that there ia a wide variety in response, even among healthy individuals. Delineation of sensitive individuals depends on observing changes in specific biological end points of greater consequence, at greater frequency, and/or at lower concentrations (*2*). In terms of definitions, there are individuals that respond with heightened reactions to lower doses; the terms used to express these reactions are sensitivity and hypersensitivity, or responsiveness and hyperresponsiveness. It appears that 5 to 20% of normal (e.g., asymptomatic, without obvious objective abnormalities) populations will be "sensitive" for a given organ system and/or a given pollutant (*2*).

As an example, certain individuals will respond to all eye irritants and at a lower dose than normal (*3*), one of the possible common hyper-neuro-responses (*4*). It is also believed (certainly by environmental allergists) that people with allergies will

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respond to many pollutants with an allergic attack. It is usually difficult to determine the cause of sensitivity, though various biological mechanisms have been studied. Frequently, those with preexisting illnesses are part of the sensitive population because they may often respond, sometimes hyperrespond, to a pollutant exposure that may not affect most people. Such preexisting conditions often are manifestations of susceptibility. [Although "susceptibility" is not distinguished from "sensitivity" by EPA (*2*), it is distinguished by others, based on the discussion that follows.

Susceptibility typically implies that the individual is endowed with some biological characteristic that may lead to an enhanced biological response. The underlying characteristic is shared usually by others in the population, and this subgroup is usually only a fraction of the general population. Susceptible individuals, when sufficiently exposed, will become sensitive (either specifically or nonspecifically) to further exposures. It is thought that the proportion of susceptible individuals increases with increasing disease frequency and relative risk but declines at high exposure frequencies (*5*). There are questions in epidemiology about chronic diseases: Can exposures be considered sufficient causes of disease? If they can, do common exposures suggest fewer susceptible individuals in the population? (*5*). Such susceptible individuals require special evaluation and attention in all exposure–response studies and risk assessments.

Asthmatics are excellent examples of individuals who were susceptible to the disease and, once inflicted, are susceptible to the effects of many environmental and nonenvironmental agents (*6–17*). Their susceptibility may have been innate (e.g., genetic) and/or induced by events/exposures in their lives (*7*). When responsive to these agents, asthmatics are considered sensitive to those agents. Thus, many asthmatics had asthmatic parents or atypical immune systems. When exposed in life to allergic or infectious agents, they were susceptible to develop asthma. If they developed asthma, they were susceptible then to the effects of these and other agents. Thus, asthmatics become sensitive to allergic agents, such as pollen, and are hyperresponsive when exposed (*7*). Interestingly, asthmatics or their families, knowing this hypersensitivity, exercise self-selection as to what habits they have and where they live, thus affecting the estimate of the "population at risk." For instance, studies of children we have performed in smelter towns in Arizona indicate a smaller proportion with asthma in such towns (*18*). It has been determined also that there are very few asthmatics in general exposed to the short-term concentrations of sulfur dioxide that produce their asthmatic attacks.

The responses of sensitive population subgroups as well as representative populations have been determined empirically in controlled human exposure and in epidemiological studies (*19–23*). Using this information and prevalence rates from epidemiological surveys, risk assessment has been conducted to model what health end points would occur in what proportion of the population and where this would occur in relation to the sources of the pollutants of concern (*2,9,24*). Information so generated can be used also for empirical validation of risk assessments; this is especially helpful because such techniques are evolving still.

Little is known with certainty regarding the effects of many of the indoor and outdoor air toxics or the complex mixtures of such toxics on either normal or sensitive populations. Changes in sensitivity may occur from cross-reactivity to pollutants (*2*). Molecular processes of interest are both genetically linked and environmentally induced biochemical and immunochemical status, as such status determines the characteristics of an individual's response to environmental exposures and subsequent disease. Immunogenetic factors of toxicological concern include: *a*) IgE (the major mediator of immediate hypersensitivity and related to resulting cellular changes and inflammation); *b*) IgA and IgG (modulators of IgE and mediators of both immunological reactions and delayed hypersensitivity to extrinsic agents); *c*) atopy (predisposition to allergy, genetically independent of IgE and indicator of prior sensitization to specific allergens); *d*) factors producing bronchial responsiveness (genetically independent of immunoglobulins and atopy, but not independent of inflammation, and interdependent with IgE and atopy as indicators of susceptibility; precursors to respiratory disease); and *e*) cellular mediators (derived from eosinophils and mast cells/basophils and linked by both specific receptors and gene-regulated mediators to the above). The results stemming from work with these molecular processes have been instrumental in the current formulations of the basis of acute and chronic respiratory diseases, especially airway obstructive diseases (AOD). Other molecular/cellular research in proteases, elastase activity, oxidants and anti-oxidants, receptors and mediators have led to a focus on the biochemical factors as they are related to susceptibility and pathogenesis. Also, social and genetic factors may influence nutritional metabolism, including the utilization of vitamins (such as E) that might affect response.

One must do further studies to determine which pollutants, in what mixtures and at what concentrations will affect those exposed. It is likely that studies could also determine which subpopulations are sensitive to which contaminants or mixtures. One would first evaluate the known factors that might influence sensitivity; this includes current status as well as past history, such as childhood respiratory troubles (*7*). There will still be "responders" (those who respond more at lower doses) who have no evidence of any of the known risk factors. These individuals are empirically "sensitive," and the cause of such sensitivity may not be found in the near future. Nevertheless, they too must be considered at risk; studies that continue to evaluate possible causes of sensitivity will, of course, be needed and should be supported.

There are several examples of the need to study the effects in the populations exposed (to determine who's at risk) of complex mixtures (and sources) for several pollutants: environmental tobacco smoke (ETS) and other combustion sources that produce particulate matter (PM) (PM_{10} = size fraction $\leq$ 10 μm, $PM_{2.5}$ = $\leq$ 2.5 μm), carbon monoxide (CO), nitrogen dioxide (NO_2), formaldehyde (HCHO), benzene; complex mixtures of organic compounds (from consumer products, building materials, humans, and other animals), and bioaerosols. More importantly, for the design and interpretation of epidemiological studies of populations at risk, there are several examples of multiple pollutants from various sources having possibly synergistic effects, often with some of the other risk factors (examples are given below).

There are other exposure (source/ventilation) factors of major current interest that would determine the population at risk due to their exposures; they include use of evaporative coolers

used for air conditioning (versus refrigeration), which is a major ventilation source in arid regions and, along with humidifiers, a major potential source of biological aerosols (due to its use of a water reservoir); dehumidifiers; air cleaners; exhaust fans; and kerosene, liquified petroleum gas and natural gas unvented space heaters, which produce high levels of air contaminants (especially oxides of nitrogen and sulfur, including acids and, in the case of kerosene heaters, particulates) (*25,26*). Other unusual use factors (e.g., stoves for heating) need to be evaluated in this context also.

Examples

Populations Exposed to Different Amounts of Ozone in the South Coast Air Basin of California

Kleinman et al. (*27*) and Kleinman (*28*) evaluated the demographics of populations living in different areas of the South Coast Air Basin of California. They then related the different demographic subpopulations to studies of time activities for those subpopulations. They related this information to concentrations found in the different areas and then to studies of indoor–outdoor ratios of ozone. These personal exposure data were related then to exercise levels in the different demographic subpopulations to obtain dose estimates for the different subpopulations in different areas. This information was then related to the biological end points that were known to occur from exposure to ozone to obtain prevalence rates. This information could be evaluated then as to the degree of excess in each of the subpopulations including those known to have prior disease (as estimated from prevalence rates of disease from surveys). The excesses were quite large, as one might expect in the Los Angeles area; the results will be published soon. The approach was a good model for determining various populations at risk based on exposure–dose and exposure–response data.

Multipollutant Studies of Sensitive Populations in Tucson, Arizona

Our studies of bronchial responsiveness in families confirmed that absolute values of peak expiratory flow rate (PEFR) are lower in children due to age and body/lung size. Variability was also greater in children (*8*), as reported previously (*11,29*). In this preliminary data set, absolute PEFR is lower in the early morning and at bedtime, and in those with chronic symptoms, even in those under age 45. Further, time of day and chronic symptoms (in adults) appear to increase diurnal and daily variability. Variability (that is, responsiveness or reactivity) appear to be higher in current adult smokers who do not have symptoms. Thus, current smokers without chronic symptoms probably have greater reactivity, as shown also by others (*30*).

Daily PEFR reactivity correlated with monitored indoor $PM_{2.5}$; (*29*) after adjusting for age and sex. In a log-linear model, the rates of reactivity were 31.6% in homes with <15 $\mu g/m^3$ and 45.4% in homes with higher concentrations. The relationship of diurnal reactivity and $PM_{2.5}$ occurred primarily in homes independent of ETS, but similarly, rates were higher in homes with more PM_{10} and ETS: in this case, PM and ETS were colinear ($p = 0.0004$) and interacted. Further, in children the prevalence rate of daily reactivity related strongly to ETS ($p = 0.0275$), and the log-linear model was significant controlling for age and sex (*31*). PEFR reactivity has been shown to relate significantly to the presence of formaldehyde at concentrations above 25 ppb (*11*). There is a synergism in the case with ETS with HCHO that occurs primarily in the low socioeconomic status (low education) households (*12*). Indoor NO_2 also affects PEFR, especially in the morning, and primarily in low socioeconomic status households, but independent of HCHO (*12*). With this technique of defining the population at risk, we have demonstrated that prevalence rates of reactivity relate to specific pollutants and to exposures to complex mixtures in children and in others with greater sensitivity.

Discussion

The contaminants of concern are respiratory irritants or allergenics; the biological aerosols are infectious or allergenic. The irritants have direct impact on cellular biochemical processes and indirect impact on the immunochemical processes/status. The infectious and allergenic agents have direct impact on the immunochemical processes and indirect impact on other cellular processes. The agents appear to act synergistically, and individuals with specific host characteristics are more sensitive or susceptible to these effects. The major pathways involve increases in airway permeability and thus cell mediators of immunity, allergy and inflammation, and direct epithelial damage leading to mediator release and inflammation (as well as damage to host defense mechanisms). Mechanisms involved include bronchial responsiveness associated with inflammation and immunoglobulins (B cells) associated with hypersensitivity. Host characteristics (genetic or environmentally induced) and these cellular processes determine susceptibility and sensitivity of response as well as disease processes. Again, these have been shown to be primarily immunochemical, cellular processes. Thus, toxicological genetic effects of contaminants are molecular/cellular processes, enhanced by environmentally induced increased susceptibility (based on biochemical and immunochemical cytoltoxicological responses). Those processes that are either well established or being studied in animals and are assumed in controlled human exposure studies can be evaluated epidemiologically.

Epidemiological studies, on the other hand, do not preclude the need for further toxicological study of pollutants that have been identified but not well characterized or that are chemically complex. Toxicological studies are needed to characterize the mechanisms and interactions of the effects and to estimate the exposure–effect relationships (e.g., organic components of tobacco smoke). For most volatile organics from solvents, cleaners, maintenance products, and sidestream tobacco smoke, the mechanisms of response are so complex and poorly understood that toxicological and also controlled exposure studies may be required before we can assess the populations at risk.

Further, some pollutant classes may be well characterized but occur in concentrations sufficient for study only in occupational settings (e.g., asbestos, some volatile organic compounds, some mineral fibers); the adverse health effects of those pollutant classes are therefore most likely to occur only in occupational settings (*7*). Field studies are needed to determine the potential

population at risk and to measure in the potential representative population at risk the magnitude of several possible exposure–response relationships (*14*).

Generally, it has been assumed that all populations exposed to complex mixtures of pollutants would be affected and would thus be at risk. However, how well are such populations at risk protected from exposures to complex mixtures indoors? One response to this question is "One can only conclude that the goal of protecting human health is not adequately served by the application of outdoor air quality standards" (*26*). Specifically, the experience gained in developing and implementing strategies for population exposure reductions in the outdoor environment is not very applicable to indoor environments. Further studies are needed to determine exposure profiles for complex mixtures indoors (*32–34*), the factors affecting exposure, and the health responses to those mixtures. Then, new strategies will need to be developed, tested, and evaluated to promote preventive policies.

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