Demographic Patterns and Human Responses to Environmental Contaminants

ANATOLI I. YASHIN, ALAN J. BERNSTEIN and JAMES W. VAUPEL

1 INTRODUCTION

Reid Smith is a cigarette-smoking New Yorker. Taylor Smith is a retired non- smoker who worked in an asbestos factory for 35 years. Jamie Smith is a pregnant housewife from a small Southern town in the U.S. Carter Smith is a farmer who consumes inadequate levels of vitamin A, vitamin E, and magnesium in his daily diet.

Despite obvious similarities in surname and nationality and, perhaps, various other similarities, their responses to identical amounts of environmental pollutants probably vary greatly.

As a cigarette smoker, Reid faces elevated risks of a variety of diseases including lung cancer and cardiovascular illness. He is probably sensitive to cadmium, hydrocarbons, lead, nickel, and radioactive compounds. As an urban dweller, he runs a greater risk of developing respiratory illnesses, and is subsequently more susceptible to a variety of respiratory irritants.

Taylor, because of his lifetime avoidance of cigarettes, runs only a minimal risk from his long-term asbestos exposure. However, because age has weakened his immune and enzyme systems, he is very possibly hypersusceptible to pesticides, PCBs, and respiratory irritants. Changes in his bone structure have also probably increased his body's retention of fluoride and thus made him more at risk to heavily fluoridated water.

Jamie's pregnancy has increased her susceptibility to carbon monoxide, insecticides, cadmium, manganese, and lead, especially if she is not taking iron or calcium supplements. Smoking would present high risks both for herself and her fetus. In addition, she very well may be absorbing unusually high levels of carbon monoxide and nitrous oxide in her kitchen.

Finally, Carter's deficiencies of vitamin A, vitamin E, and magnesium make him a high risk for exposure to DDT, hydrocarbon carcinogens, PCBs, lead, ozone, and fluoride. If he suffers from G-6-PD deficiency, a red blood cell disorder, his concurrent vitamin E deficiency probably makes him extremely sensitive to erythrocyte oxidant stress and to hemolytic precipitators such as ozone.

Methods for Assessing Exposure of Human and Non-Human Biota. Edited by R.G. Tardiff and B. Goldstein

It is generally accepted that the risk of disease and death vary markedly by age and sex. However, there are also inherited and acquired factors that cause vast differences in human susceptibility to many pollutant exposures. Most people are less familiar with this wide range of heterogeneity precipitated by genetic make-up, life style, occupation, nutrition, residence location, and other factors. The combined role of these many heterogeneity factors is often underestimated. Yet they are the major factors that determine the evolution of mortality and morbidity patterns within a population.

In this paper, we examine a variety of heterogeneities present in environmental pollutant susceptibilities, briefly look at how attempts to recognise heterogeneity have played a role in efforts to regulate pollutants, consider how likely shifts in the composition of a population that may affect morbidity and mortality relate to environmental pollution, and conclude with a discussion of how indirect heterogeneity factors can lead to additional complications in interpretations of pollution-related mortality statistics.

2 INFLUENCE OF AGE ON POPULATION SUSCEPTIBILITIES TO CHEMICALS

Age is one of the primary causes of differential susceptibility. Particularly for the very young and the very elderly, there exists a variety of significant dangers which may pose little or no threat to those in other life stages.

Immature immune systems and enzyme detoxification systems of infants and children reduce the ability of their body to rid itself of environmental pollutants. Many pollutants have minimal effects on healthy adults, but, in children, can accumulate in the body relatively unimpeded. This helps explain why PCBs, often present in high levels in mother's milk, are particularly dangerous to breast-fed infants at the precise time when they are least able to process this dangerous environmental pollutant, their diet contains higher levels of PCBs than the diet of any other age group.

Children up to approximately age 10 also suffer from a deficiency of immunoglobulin A (IgA). This is the primary immunoglobulin in tears, saliva, nasal, bronchial, and gastrointestinal secretions (Eisen, 1974; Koistinen, 1975). IgA deficiency is widely believed to be a strong contributing factor in upper and lower respiratory infections. Confirming this hypothesis are studies showing that children who live in more heavily polluted areas have been found to suffer higher rates of respiratory infections than those living in areas with fewer respiratory irritants (Fosburgh, 1974).

Newborns up to three months old also have low levels of enzyme superoxide dismutase (SOD), generally around 65 to 80 percent of adult levels (Legge *et al.*, 1977; Rotilio *et al.*, 1977; Ueda and Ogata, 1978). SOD is one of the body's chief protective mechanisms against high concentrations

of sulfur dioxides, radiation, ozone, nitrogen dioxide, and paraquat. Inferior levels of SOD leave infants at highly elevated risks to the toxicity of these environmental agents.

Common nutritional deficiencies also leave children hypersusceptible to a variety of environmental pollutants. Ninety-eight percent of children between ages of 2 and 3 years receive less than the recommended daily allowance (RDA) of iron. This is believed to increase their risk of toxicity from hydrocarbons, lead, and manganese. Sixty-five percent of children between these ages also receive less than their RDA of calcium, increasing their susceptibility to lead. The 10 to 30 percent of infants and children who receive sub-RDA levels of vitamin C have elevated susceptibilities to arsenic, cadmium, carbon monoxide, chromium, DDT, dieldrin, lead, mercury, nitrites, and ozone. And the 25 percent of children ages 7 to 12 who have sub-RDA levels of vitamin A in their diet are at increased risk of toxicity from DDT, hydrocarbon carcinogens, and PCBs (Calabrese, 1978).

Certain unique susceptibilities exist for women in their child-bearing years. Oral contraceptive use, when combined with cigarette smoking, poses a particular threat. Among women under 50 years old who smoked 35 or more cigarettes a day and used oral contraceptives, the rate of myocardial infarction was estimated to be 20 times higher than among those who had never smoked.

In Great Britain between 1958 and 1971, the death rate for women aged 35 to 44 years old increased by over one-third. During this time, cigarette smoking by women in the age group increased by 35 percent and contraceptive pills came into popular use.

Another set of increased risks face the aged. Like children, the elderly also suffer from relatively ineffective immune and enzyme systems, and suffer increased susceptibilities to many of the same environmental pollutants as the very young.

3 DIFFERENCES IN BIOLOGICALLY STIPULATED SUSCEPTIBILITIES TO CHEMICALS

A variety of pre-existing health conditions also produces several more heterogeneities in susceptibility to environmental pollutants. Individuals with asthma are unusually susceptible to respiratory irritants such as nitrogen dioxide, ozone, sulfates, and sulfur dioxide. People with cystic fibrosis are also at high risk from ozone and other respiratory irritants. Diabetics are much more likely to have negative reactions to large, single doses of radiation. Sickle cell anemics run greater risks from exposure to aromatic amino and nitro compounds, carbon monoxide, and cyanide (Calabrese, 1978).

Other less apparent, largely genetic health factors are also believed to

play a major role in the great variety that exists in individual susceptibility to pollutants. Rates of aryl hydrocarbon hydroxylase (AHH) inducibility, a genetically controlled factor, are thought to be a key indicator of lung cancer susceptibility. It is thought that most chemical carcinogens must be metabolically converted into their carcinogenic form, and higher levels of AHH inducibility have been connected with significantly elevated lung cancer rates (Calabrese, 1978).

Population frequencies of AHH inducibility have been determined. Among the United States' white population three distinct groups have been categorised: low (53 percent), intermediate (37 percent), and high (10 percent) inducers (Kellermann *et al.*, 1973). Kellermann's studies of bronchogenic carcinoma patients revealed that the intermediate and high AHH inducibility cohorts had 16 and 36 times greater risk of lung cancer than the low AHH inducibility group.

Particularly suggestive from a policy viewpoint are Kellermann's findings of strong positive correlations between smoking, high inducibility, and high rates of lung cancer, and also between smoking, low inducibility, and relatively low rates of lung cancer. This offers an intriguing insight into why it is possible for some heavy smokers to never develop any signs of lung cancer, while relatively light smokers may succumb to lung cancer at an early age. Since there are tests for AHH inducibility, it may be advisable to set up screening clinics for smokers (as well as those considering starting smoking) to give them a greater insight into the risks to which they may be subjecting themselves.

Another human genetic disorder, glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, may be a key causal factor in the high susceptibility some individuals have to hemolytic stress conditions. G-6-PD is a red blood cell enzyme needed to maintain erythrocyte membrane integrity. G-6-PD deficiency in male subjects is revealed by sensitivity to primaquine. Approximately 11 percent of American black males suffer from G-6-PD deficiency (Beutler, 1972), as do 11 percent of Mediterranean Jews, 12 percent of Filipinos, and 2 to 5 percent of Chinese (Lazarow, 1954; Stokinger and Mountain, 1963).

Under hemolytic stress conditions such as exposure to most anti-malarial drugs, many industrial chemicals, some pre-existing organic diseases, and a variety of other environmental exposures, G-6-PD deficients may develop hemolytic anemia and be unusually sensitive to lead toxicity. It may be useful, although politically sensitive considering the distinct racial component of the disease, to screen for G-6-PD among those who work extensively with a variety of common chemicals.

Thalassemia is another genetic red blood cell disorder which may produce heterogeneous susceptibility, an abnormality in the rate of hemoglobin synthesis. Thalassemia is especially frequent among people living in the

Mediterranean region, the Middle East, and the Orient (Silvestroni and Bianco, 1959).

As screening for thalassemia has only occurred infrequently, there are few reports relating its occurrence with pollutant reactions. However, it is suspected that thalassemia aggravates lead (Toche *et al.,* 1960; Jonderko, 1961) and benzene toxicity (Saita and Moreo, 1959).

A final area of biological susceptibilities, intriguing in their universality, are circadian rhythms: the twenty-four hours cycles which occur in cell growth, mitosis, hormonal levels, body temperature, and a variety of other human functions. These rhythms are suspected of playing an important role in heterogeneous susceptibility (Luce, 1970; Halberg, 1960).

If all people have certain periods of the day during which they suffer increased susceptibility, then workers who are employed in switch shift occupations (medicine, police, fire, industry) may be regularly placed into high risk situations. Additional studies have shown that some individuals are never able to completely adjust their circadian rhythms to their work habits (Felton and Patterson, 1971; Teleky, 1943). It would seem desirable for these people to avoid work shifts falling in their high susceptibility periods.

4 MANY HETEROGENEITY FACTORS ARE ACQUIRED

Another important area of cohort susceptibilities involves those factors not inborn, but acquired by selected lifestyle. Among these factors, the most important is smoking which is by far the greatest controllable factor in lung cancer susceptibility. It also affects risk levels for a variety of other diseases such as bronchitis, emphysema, and cardiovascular illness. In addition to making its own contribution to mortality and morbidity rates, smoking, when combined with a variety of other factors, can exert a substantial influence on risks from exposure to environmental pollutants. Numerous studies have led to the conclusion that the effects of smoking and environmental air pollution, when both are present, cause more than an additive increase in susceptibility (Stern, 1977).

Cigarettes are a major producer of carbon monoxide. A frequent CO exposure level for community air pollution is 10 to 30 parts per million (ppm), or 11 to 33 mg/m^3, over 4 to 8 hours. In contrast, five minutes of frequent repetition smoking, considered to be a representative dose, causes an exposure level of 400 ppm (440 mg/m^3) (Stern, 1977).

A high positive correlation has been found between smoking, increased pollution levels, and the incidence of bronchitis. High air pollution levels have been found to have little effect on incidences of serious bronchitis among non-smokers (Stern, 1977).

Smoking may significantly affect diabetes. There is research indicating a significant relationship, particularly for male diabetics, between smoking patterns and incidence of diabetic nephropathy, the most frequent cause of death in young diabetics (Christiansen and Nerup, 1978). Smoking is also believed to increase a diabetic's need for insulin and to significantly increase the risk of glomerulosclerosis and retinopathy (West *et al.,* 1980).

Smoking can also cause the development of vitamin C deficiency. Nicotine has been found to significantly reduce the ascorbic acid content of human blood. Thus, both smokers as well as infants who are breastfed by mothers who smoke run elevated risks of vitamin C deficiency related susceptibilities.

The age a smoker develops his habit is correlated negatively with the disease risks. The fourth World Congress on Smoking and Health, held in Stockholm, concluded that the younger a person is when he starts to smoke, the higher the risk of disease. Lung cancer rates of men in their fifties who began smoking when they were thirteen are 40 percent greater than rates for men who began smoking at age 17. Continuing this trend, a man who began to smoke at age 27 has only 20 percent the probability of developing lung cancer of a man who began at age 17.

The dangers of smoking are not exclusively limited to the smoker. Maternal smoking during pregnancy has been determined to retard fetal growth. The average weight of a smoking mother's newborns is 200 grams less than that of offspring of non-smoking mothers. Follow-up studies of infants born to smoking mothers have shown some continuing effects through age 7. Following an examination of 12,000 patients, it was reported that smoking mothers are more likely to have spontaneous abortions, premature deliveries, and pre-natal loss than non-smoking mothers.

An infant's susceptibility to bronchitis or pneumonia in the first year of life is doubled if the child's parents smoke. Wheezing up to age five is also more common in those individuals.

Inadequate nutrition increases pollutant susceptibility for an extremely large segment of the population. Adequate nutrition may be one of the best ways to decrease an individual's risks to a wide variety of environmental pollutants. For instance, an inadequate dietary level of vitamin E can significantly heighten susceptibility to erythrocyte oxidant stress in a G-6-PD deficient person.

Nutrition deficiencies, caused by a variety of factors including heterogeneous nutritional needs, are particularly prevalent among lower-income groups. In the U.S., roughly a quarter or more of this cohort suffers from deficiencies of vitamins A and C, leading to elevated susceptibilities to hydrocarbon carcinogens, DDT, PCB, arsenic, cadmium, carbon monoxide, chromium, dieldrin, lead, mercury, nitrites, and ozone (Calabrese, 1978). In an interesting circular response, exposure to PCBs, DDT, and dieldrin can exacerbate Vitamin A deficiency. A strong negative correlation has

been found for vitamin A levels and lung cancer rates, even with matched smoking patterns (Calabrese, 1978).

Other nutritional deficiencies cut across poverty lines. For instance, most U.S. males have a partial magnesium deficiency which leaves them at increased risk to fluoride toxicity; people with kidney diseases often have inadequate phosphorus levels and are susceptible to lead toxicity; many women and some men ingest less than two-thirds of the RDA for riboflavin and risk greater harm from exposure to hydrocarbon carcinogens, lead, and ozone (Calabrese, 1978).

Pregnancy is another important pollutant risk factor. Numerous physiological changes in a woman's body during pregnancy increase the risks posed to her from a variety of environmental pollutants. Some of the biggest changes affect nutritional requirements, particularly for calcium and iron. Researchers have reported anemia in 15 to 58 percent of pregnant women. These deficiencies would consequently make pregnant women hypersusceptible to the toxic effects of manganese, cadmium, and lead.

Endogenous CO production can increase dramatically during pregnancy. Given already high levels of carbon monoxide, pregnant women are at heightened risk from exposure to environmental and smoking CO.

Pregnant women have also been shown to be at greater risk to exposure to DDT and other insecticides. DDT-exposed workers have significantly higher levels of childbearing disruptions such as spontaneous miscarriage, pregnancy toxicosis, and premature bursting of the amniotic sac.

Occupation-related susceptibility effects face not only pregnant workers. Radon-exposed uranium miners have been found to have elevated levels of lung cancer, and when smoking habits are taken into account, the positive correlation between radon exposure and smoking appears to produce a multiplicative, rather than additive, effect. Similarly, coal workers who smoke have significantly higher incidences of emphysema and heart disease when compared with non-smoking coal workers (Calabrese, 1978).

The most extensive occupation-heterogeneity research has been done for asbestos-exposed workers as far back as the 1920s. Links between lung cancer and asbestos have been suspected since the late 1940s. Studies have shown that after 20 years of exposure, mortality rates of asbestos workers are double those of the general population.

Approximately 20 percent of all asbestos workers die of lung cancer. However, non-smoking asbestos workers do not suffer unusually high levels of lung cancer. Selikoff's study concluded that an asbestos worker who smoked had 92 times the chance of dying of lung cancer of non-smoking asbestos workers.

Not only do smoking asbestos workers have elevated lung cancer rates, but also so do ex-smoking asbestos workers. While the occurrence of lung cancer is lower among ex-smokers than smokers, it is still considerably

higher than among non-smokers. This would tend to undermine the prevalent belief that the ill effects of smoking can, with time, be completely overcome, and instead support the heterogeneity-based idea that the most susceptible smokers tend to die within ten to twenty years after quitting their habit; it is the surviving ex-smokers who never faced particularly great danger from their past habit.

Asbestos exposure also increases an individual's risk of obtaining mesothelioma, a rare tumour of the chest or abdominal cavity. Most sufferers of mesothelioma have been exposed to asbestos. Mesothelioma is not always occupation-related, however. High incidences have been reported in residences near industries where asbestos was used; also there is a statistical excess of mesothelioma and other asbestos-related diseases among household members of occupationally-exposed workers.

Alcohol is another major behavioral influence in heterogeneous susceptibility to environmental pollutants. Detoxification of alcohol places considerable strain on the human liver and can cause permanent damage over a period of years. As the liver is also needed for the detoxification of a variety of pollutants (insecticides, lead, etc.), impairment of the liver increases the risk of these substances (Calabrese, 1978).

Alcohol abuse is also believed to be an influence on cancer susceptibility. Not only has alcohol been found to increase the probability of acquiring lung cancer but, when accompanied by smoking, there is believed to be a synergistic, rather than additive, increase in cancer risks.

Finally, positive correlations have been found between urban residence and respiratory illness. The Three City Study found a persistent excess in urban dweller's lead levels as compared to rural populations. Lead is believed to cause anemia and hyperactivity in children.

Acute air pollution episodes are a primarily urban occurrence. In these incidents, extraordinary meteorological conditions will lead to an effective reduction in air volume, causing a rise in local pollution levels. Small water droplets, often fog, have caused what is essentially a rain of pollution. Acute air pollution incidents have been associated with excess mortality and morbidity. During the past 50 years, there have been acute air pollution episodes in London, New York City, New Orleans, Minneapolis, and Tokyo.

5 POPULATION HETEROGENEITY AND THE REGULATION OF CHEMICALS

Legislation to regulate industrial and environmental pollution has traditionally made a limited attempt at recognizing heterogeneous susceptibility through calls to protect the most pollution-sensitive groups within a population. For instance, infant susceptibility to nitrate and nitrite toxicity played a key role in the formulation of drinking water standards for those compounds.

Still a confusion of goals remains apparent in this body of legislation. The confusion is fueled in part through uncertainty over how it is best to handle multi- level risk situations: should the goal of environmental policy makers be to remove dangerous pollutants from the environment? or to allow dangerous pollutants, but remove susceptible individuals from the environment? While the intuitive sympathy lies against restricting opportunities for high-risk individuals, there are convincing economic arguments for limited access to certain industrial jobs when high risk individuals can easily be classified and reassigned. Attempts to screen for susceptible workers in the job market are becoming more common.

Legislation such as the Clean Air Act of 1969 mandated the establishment of threshold values to protect the most sensitive individuals from risk from environmental pollutants. Yet threshold limit values are a continuous source of controversy: is there any level below which all individuals are safe?

Even when establishing threshold limits, the government has often acted on the assumption that high risk groups comprise minute segments of the entire population (Calabrese, 1978). Actually all individuals, at certain points in their lives, belong to some high risk group. To ignore the hypersusceptible individual in formulating standards may eventually ignore the entire population.

The Occupational Safety and Health Act (OSHA) of 1970 added to the importance of identifying the most susceptible workers by mandating that no worker develop exposure-related health impairments. The Toxic Substances Control Act (TSCA) of 1976 introduced a more subtle recognition of heterogeneous response into environmental legislation. Rather than ignoring the broad implications of varied susceptibility, or searching for an illusory risk cut-off, this act calls for the inclusion of cost/benefit analysis in determining acceptable levels for new substances.

6 DEMOGRAPHIC TRENDS CAN MASK PROGRESS AGAINST POLLUTION

Having examined some of the heterogeneities most likely to be involved in varied susceptibility to environment substances, it would seem that knowledge about risk variation could be applied to major demographic changes to make some predictions about impending alterations in mortality statistics.

The aging of a population will probably result in confusing signals about man's progress against environmental pollutants. The greatest success against mortality in recent years has been achieved against heart and circulatory disease. As people have been living beyond what would, in prior years, have been their heart-related mortality, more are contracting cancer, a disease in which most success against morbidity and mortality has occurred at the younger ages. If the increasing number of elderly with weakened

enzyme and immune systems suffer even higher rates of pollutant-related cancer mortality, it will become important to consider the likelihood the elderly would have had at an early age, of dying from circulatory illness, so as not to interpret this new demographic trend in a purely negative light.

Increased urbanisation may also affect pollutant mortality rates, particularly in terms of respiratory illness. Increased urbanisation and the growing number of elderly persons may offer a convincing argument for immediately increasing research and other efforts against respiratory disease.

The move toward greater automation in the manufacturing sector and the growth of service jobs may help to lower pollutant-related deaths as workers are removed from continuous, long-term exposure to harmful pollutants and chemicals. However, indoor pollution in hermetically-sealed office buildings has the potential to become a major health concern, and it should not be presumed that moving workers out of manufacturing will automatically move them towards greater health.

7 HETEROGENEITY AND UNEXPECTED DEMOGRAPHIC TRENDS

While major shifts in a population have direct affect on the incidence of environmental pollutant-related illnesses, a variety of other possible changes may have strong indirect effects on mortality and morbidity rates (Vaupel and Yashin, 1985a, b).

If, for instance, some chemicals react with acquired heterogeneities, then tighter pollution controls will change heterogeneity distribution in the population. If this occurred, one might observe changes in mortality patterns. The new mortality rate will grow faster with age than before the intervention. One may even observe convergence or even cross-over of these mortality curves.

If a pollutant is responsible for a particular cause of death, its elimination will not necessarily lead to increases in life expectancy at every age. It is possible that some pollutants increase mortality almost exclusively among the most frail individuals, thus promoting an intensive selection process. Removing this pollutant would decrease the mortality rate for some age groups, yet at the same time mortality rates might rise significantly within the next age interval, leading consequently, to a lowered life expectancy estimate at that age.

Some heterogeneity factors such as smoking, alcohol consumption, and inadequate nutrition can be responsible for a multivariate impact on human organisms and produce different causes of death; therefore, medical progress against one particular cause of death in the presence of this contaminant can increase the observed mortality from another cause of death.

If there are several contaminants each responsible for several causes of

death, then non-uniform progress against cause-specific mortality could also produce a decline in some mortality rates and growth in others. Non-uniform progress toward lowering pollution levels can produce additional unexpected effects on the population morbidity. For some diseases rates will decline, for others they will rise.

If it is assumed that tighter pollution controls will have their greatest effect on reducing cancer incidences, these controls could eventually lead to an increase either in cardiovascular deaths or to a rise of major new groups of mortalities. Decreased smoking would also tend to have the same result.

Impressive progress has been made against cardiovascular illness in recent years. The largest remaining area for a health breakthrough may well be cancer among higher age groups. If breakthroughs comparable to those in treating circulatory disease occur in this field, the carcinogenic effects of environmental pollutants would become, *de facto*, less significant. Assuming that the susceptibility was decreased relatively equally throughout the population, progress against cancer might well increase the importance of hypersusceptible cohorts with other ailments. As they became increasingly the only people to suffer from environmental pollutant-related mortality, their problems would automatically draw greater attention and assume higher priority in the policy field.

8 MODELING HETEROGENEITY

Heterogeneity models use two sets of assumptions. One involves the functional form of the hazard function; the other is concerned with the probabilistic distribution of heterogeneity factors.

If the variables that influence hazard rates can be observed, one is dealing with observed heterogeneity. There are several functional forms often used to specify the hazard functions. One of the most widely used recently is the proportional hazard model. In it, the hazard rate $h(t,z)$ can be described in terms of the product of the two functions: $l(t)$, which depends only on time at age t, called the underlying hazard and $u(z)$, which depends only on the influential variable.

$$h(t,z) = \lambda(t)u(z) \tag{1}$$

In the Cox (1972) model, $u(z)$ takes the form

$$u(z) = e^{\alpha z} \tag{2}$$

variable z would specify, for instance, the level of the environmental pollution in some particular area.

Vaupel *et al.* (1979) and Vaupel and Yashin (1985a) focused on the analysis of hidden heterogeneity in the model where hazard functions can be represented in the form

$$h(x,z) = zu(t) \tag{3}$$

The combination of observed and unobserved heterogeneity in hazard functions was analyzed in Heckman and Singer (1982) for some econometric models. Vaupel and Yashin (1985b) analyzed some unexpected effects of heterogeneity on population dynamics. Yashin *et al.* (1985) considered the stochastic process models of mortality and aging in the presence of heterogeneity that can change over time. The continuous time and continuous state stochastic process was considered as a model for influential factors. The finite state jumping process model was analyzed in Yashin (1984). Estimation procedures and forecasting algorithms were also analyzed in Yashin *et al.* (1985, 1986).

9 CONCLUSIONS

In considering and implementing environmental pollution controls, an understanding and appreciation of the important role played by human heterogeneity may be one of the keys to producing successful policy. Heterogeneity, both biological and acquired, can lead to significant variety in individual susceptibility. It is conceivable that one individual might be at no risk to the harmful properties of a pollutant, while another individual might face greatly increased levels of mortality from even low-level, infrequent exposure. Thus, while recent legislative attempts to limit environmental pollution have increasingly recognised the significance of heterogeneous risk cohorts, much can still be done to take differing risks into account.

Heterogeneity also plays an indirect role in man's study of environmental pollution. Competing risks can confuse interpretation of statistics related to man's progress against pollution, and the independent increase or decrease of different risk groups can cause a corresponding drop or rise in morbidity or mortality. To help predict the importance of such changes, heterogeneity can be modeled in a variety of ways to give greater insight into the effect of changes among different cohorts.

10 REFERENCES

Beutler, E. (1972). Glucose-6-phosphate dehydrogenese deficiency. In Stanbury, J.B., Wyngaarden, J.B. and Fredrickson, D.S. (Eds.) *The Metabolic Basis of Inherited Disease*, 3rd edition. McGraw-Hill, New York.

Calabrese, E. (1978). *Pollutants and High Risk Groups: The Biological Basis of Increased Human Susceptibility to Environmental and Occupational Pollutants.* John Wiley & Sons, New York.

Christiansen, J.S. and Nerup, J. (1978). Smoking and diabetic nephropathy. *Lancet* **1**, 605.

Cox, D.R. (1972). Regression models and life-tables (with discussion). *J. Royal Statist. Soc. B.* **34**, 187–221.

Eisen, H. (1974). *Immunology: An Introduction to Molecular and Cellular Principles of the Immune Response.* Harper & Row, New York.

Felton, G. and Patterson, M.G. (1971). Shift rotation is against nature. *Am. J. Nurs.* **71**, 4, 760. Fosburgh, L. (1974). Bad Air's Effect on Young Assayed. *New York Times*, December 12.

Halberg, F. (1960). The 24-hour scale: A time dimension of adaptive functional organisation. *Perspect. Biol. Med.* **3**, 4, 491.

Heckman, J.J. and Singer, B. (1982). Population heterogeneity in demographic models. In Land, K. and Rogers, A. (Eds.) *Multidimensional Mathematical Demography.* Academic Press, New York.

Jonderko, G. (1961). Diagnostic value of the determination of the blood glutathione level in chronic lead poisoning in human subjects. *Pol. Arch. Med. Wewn.* **31**, 647.

Kellermann, G., Luyten-Kellermann, M. and Shaw, C. (1973). Genetic variation of aryl hydrocarbon hydroxylase in human lymphocytes. *Am. J. Human Genet.* **25**, 327–331.

Koistinen, J. (1975). *Studies of Selective Deficiency of Serum IgA and its Significance in Blood Transfusion.* Doctoral Dissertation, University of Helsinki.

Lazarow, H. (1954). Relation of Glutathione to Hormone Action and Diabetes. In Colowick, S. (Ed.) *Glutathione.* Academic Press, New York.

Legge, M., Brian, M., Winterbourn, C. and Carrell, R. (1977). Red cell superoxide dismutase activity in the newborn. *Aust. Paediatr. J.* **13**, 25–28.

Luce, G.G. (1970). *Biological Rhythms in Psychiatry and Medicine.* USDHEW Publ. No. 2088. U.S. Department of Health, Education and Welfare. Available from National Technical Information Service (NTIS), Springfield, Virginia 22151.

Rotilio, G., Rigo, A., Bracci, R., Bagnoli, F., Sargentini, I., and Brunori, M. (1977). Determination of red blood cell superoxide dismutase and glutathione peroxidase in newborns in relation to neonatal hemolysis. *Clin. Chim. Acta* **81**, 131–134.

Saita, G. and Moreo, L. (1959). Thalassemia and occupational blood disease: I. Thalassemia and chronic benzol poisoning. (Talassemia e omopatie professional). *Med. Lavoro* **50**, 25.

Silvestroni, E. and Bianco, I. (1959). The Distribution of the Microcythaemias of Thalassemias in Italy: Some Aspects of the Haematological and Haemoglobinic Picture in These Haemopathies. In Jonxis, J.N.P. and Dolafresnaye, J.F. (Eds.) *Abnormal Haemoglobins - A Symposium:* Blackwell, Oxford.

Stern, A.C. (1977). *Air Pollution: The Effects of Air Pollution.* Academic Press, New York.

Stokinger, H.E. and Mountain, J.T. (1963). Test for hypersusceptibility to hemolytic chemicals. *Arch. Environ. Health* **6**, 57.

Teleky, L. (1943). Problems of night work: Influence on health and efficiency. *Ind. Med.* **12**, 758.

Toche, L., Lejeune, F., Tolat, F., Mauriquand, C., and Baron, M.M. (1960). Lead poisoning and thalassemia. *Arch. Mal. Prof.* **21**, 329.

Ueda, K. and Ogata, M. (1978). Levels of erythrocyte superoxide dismutase activity in Japanese people. *Acta Med. Okayama* **32**, 393–397.

Vaupel, J.W. and Yashin, A.I. (1985a). The deviant dynamics of death in heterogeneous populations. In Tuma, N. (Ed.) *Sociological Methodology 1985*, pp. 179–211. Jossey-Bass, San Francisco, California.

Vaupel, J.W. and Yashin, A.I. (1985b). Heterogeneity's ruses: Some surprising effects of selection on population dynamics. *Am. Statist.* **39**, 176–185.

Vaupel, J.W., Manton, K.G., and Stallard, E. (1979). The impact of heterogeneity in individual frailty on the dynamics of mortality. *Demography* **16**, 439–454.

West, K.M., Erdreich, L.S., and Stober, J.A. (1980). Absence of a relationship between smoking and diabetic microangiopathy. *Diabetes Care* **3**, 250–252.

Yashin, A.I., Manton, K.G., and Vaupel, J.W. (1985). Mortality and aging in a heterogeneous population: A stochastic process model with observed and unobserved variables. *Theor. Popul. Biol.* **27**, 154–175.

Yashin, A.I., Manton, K.G., and Stallard, E. (1986). Dependent competing risks: A stochastic model for mortality forecasting. *J. Math. Biol.* **24**, 119–141.