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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, the responses of these four people to exposure 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 flouride and thus made him more at risk to heavily flouridated 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 flouride. 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.

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, etc.

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 recognize heterogeneity have played a role in efforts to regulate pollutants, consider how likely shifts in the composition of population may affect morbidity and mortality rates affected by environmental pollution, discuss how indirect heterogeneity factors can lead to additional complications in interpretations of pollution-related mortality statistics, and offer several suggestive models of heterogeneous susceptibility.

2. DIFFERENT AGE GROUPS IN THE POPULATION HAVE DIFFERENT SUSCEPTIBILITIES TO ENVIRONMENTAL POLLUTANTS

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

Infants' and children's immature immune systems and immature enzyme detoxification systems reduce their body's ability to rid itself of environmental pollutants (Calabrese 1978). Many pollutants that have minimal effects on healthy adults, can, in children, accumulate in the body relatively unimpeded. (This helps explain why PCB, often present in high levels in mother's milk, is 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 PCB than the diet of any other age group.)

Children up to approximately age ten also suffer from a deficiency of Immunoglobin 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 also have low levels of enzyme superoxide dismutase (SOD), generally around 65-80 percent of adult levels (Ueda and Ogata 1978; Rotilio et al. 1977; Legge et al. 1977). Enzyme SOD is one of the body's chief protection mechanisms against high concentration dioxides, radiation, ozone, nitrogen dioxide, and paraquat. Inferior levels of enzyme 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 2 and 3 receive less than the recommended daily allowance (RDA) of iron. This is believed to increase their risk of reaction to hydrocarbon carcinogens, 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 10-30 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 to DDT, hydrocarbon carcinogens, and PCBS.

Certain unique susceptibilities exist for women in their child-bearing years. Oral contraceptive use, when combined with cigarette consumption, poses a particular threat. Among women under 50 years of age 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 35-44 increased by over a third. During this time, cigarette consumption 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 (Calabrese 1978).

3. PEOPLE DIFFER IN THEIR BIOLOGICALLY STIPULATED SUSCEPTIBILITIES TO ENVIRONMENTAL CONTAMINANTS

A variety of pre-existing health conditions also produce several additional 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.

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).

The population frequencies of AHH inducibility have been determined. Among the United States' white population three distinct groups have been categorized: 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, respectively, 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 AHH inducibility can be tested for, 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 2-5 percent of Chinese (Stokinger and Mountain 1963; Lazarow 1954).

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 deficiency 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 hour 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) are being regularly forced 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. Cigarette consumption is almost certainly 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 also a major producer of carbon monoxide. A frequent CO exposure level for community air pollution is 10-30 parts per million (ppm) (11-33 mg/m^3), over 4-8 hours. In contrast, five minutes of frequent repetition smoking, considered to be a representative dose, will cause 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 incidence of bronchitis. Tellingly, high air pollution levels have been found to have little effect on incidences of serious bronchitis among nonsmokers (Stern 1977).

Smoking may significantly affect diabetics. 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 believed to increase a diabetics 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 (McCormick 1952; Andrzejewski 1966).

The age a smoker develops his habit is negatively correlated to the risks the smoker faces. The IV 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 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, Murphy found 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.

Inadequate nutrition increases pollutant susceptibility for an extremely large segment of the population. Adequate nutrition may be one of the best ways to decrease individuals' risks to a wide variety of environmental pollutants. For instance, an inadequate dietary level of vitamin E can significantly heighten a G-6-PD deficients susceptibility to erythrocyte oxidant stress (Calabrese 1984).

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 vitamin A and vitamin C, leading to elevated susceptibilities to hydrocarbon carcinogens, DDT, PCB, arsenic, cadmium, carbon monoxide, chromium, dieldrin, lead, mercury, nitrites, and ozone (Calabrese 1978,1980). 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.

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 flouride; 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.

Pregnancy is another important pollutant risk correlative. The 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 (de Leeuw et al 1966). 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 (Hunt 1975). Given already high body 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 (Veis 1970).

Occupation-related susceptibility effects do not only face 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 (Stern 1977). Similarly, coal workers who do 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, W.E. Cooke in the *British Medical Journal* discussed the apparent dangers involved in asbestos exposure. Links between lung cancer and asbestos have been suspected since the late 1940s (Merewether 1949). Studies have shown that after 20 years of exposure, asbestos workers mortality rates are double those of the general population.

Approximately 20 percent of all asbestos workers die of lung cancer (Selikoff et al. 1964). 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, quite significantly, 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 (Selikoff and Hammon 1975). 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 a ten to twenty year period after quitting their habit, and 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 tumor 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 were used, and there is also a statistical excess of mesothelioma and other asbestos-related diseases among household members of occupationally-exposed workers (Stern 1977).

Alcohol is another major behavioral influence in heterogeneous susceptibility to environmental pollutants. Detoxification of alcohol places considerable strain on the human liver and can, over a period of years cause permanent damage. As the liver is also needed for the detoxification of a variety of pollutants (insecticides,lead,etc.), the 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 (Rothman 1975).

Finally, positive correlations have been found between urban residence and respiratory illness. The Three City Study found a persistent excess in urban dwellar'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 meterological conditions will lead to an effective reduction in air volume, causing a rise in local pollution levels. Small water droplets, often fog, have then 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 to name several (Stern 1977).

5. UNDERSTANDING POPULATION HETEROGENEITY IS IMPORTANT FOR THE REGULATION OF INDUSTRIAL AND ENVIRONMENTAL POLLUTION

Legislation to regulate industrial and environmental pollution has treated heterogeneity in a variety of ways. Some acts have explicitly recognized heterogeneity, others have implicity recognized it, while others have ignored heterogeneity, concentrating instead on engineering-based solutions.

A major group of laws which explicitly recognize heterogeneous susceptibility are those with mandates to protect the most pollutant-sensitive groups within the population. For instance, infant susceptibility to nitrate and nitrite toxicity played a key role in the formulation of drinking water standards (Calabrese 1978). Another example is the Clean Air Act of 1969 which calls for the establishment of threshold levels of pollution low enough to protect "the most sensitive group" against the "first adverse health effect" (Vaupel 1983). The U.S. Environmental Protection Agency (EPA), in setting a wide variety of national ambient air quality standards which are based on this act has repeatedly had to consider such threshold levels.

Other acts have implicitly recognized heterogeneity, setting standards that require research into varied susceptibility. For instance, the Occupational Health and Safety Act of 1970 simply orders that no worker develop exposure-related health impairments (Vaupel 1983). To enforce such an act, it is necessary to determine the sensitivity of the most-sensitive worker.

In a different way, the "zero risk" approach—if something is risky, ban it--can also be seen as a recognition of heterogeneity if the motivation for complete removal is that, for the most sensitive individuals, no safe level exists. In setting a zero standard for food additives that might cause cancer, the Delaney clause of the Federal Food, Drug, and Cosmetic Act apparently taking into account that no absolutely safe level exists for all individuals (Vaupel 1983) and thus is indirectly influenced by heterogeneity considerations.

The Toxic Substances Control Act of 1976 introduces a more subtle implementation of heterogeneous consideration by calling for the inclusion of cost-benefit analysis in determining acceptable levels of new substances. Rather than automatically seeking a point which protects even the most susceptible individual, this act allows for the consideration of trade-offs between the increasingly greater economic costs involved in protecting more and more sensitive individuals.

Other environmental pollutant acts, however, have ignored the importance of heterogeneous susceptibility. The "natural levels of risk" approach seeks levels of pollution no greater than would exist in the environment without man's intervention. Vaupel (1983) points out that such standards have been proposed to determine allowable levels of nuclear waste. Such limits do not take into account individual differences, assuming instead in this case that as man as developed in the presence of radiation, low levels of radiation must present no great danger to him.

Several "engineering" pollution standards—that is, ones which seeks to control pollution not by examining its health implication, but instead by considering the mechanics of solving the problem—also overlook heterogeneity. For instance a number of pollutants have been limited to lowest detectable levels. Vinyl chloride, which is believed to cause liver cancer, has been restricted by OSHA to an exposure level of 1.5 parts per million. This is a slight adaptation of the OSHA mandate which requires employees to be protected to "the extent feasible." This "feasibility" level has also been used in such areas as air pollution control which calls for the use of the "best practicable control technology" (Vaupel 1983).

6. CURRENT DEMOGRAPHICAL TRENDS CAN MASK THE PROGRESS AGAINST ENVIRONMENTAL POLLUTION

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

The aging of the 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, as would seem likely, higher and higher rates of pollutant-related cancer mortality, it will become important to consider the prior likelihood the elderly would have had of dying from circulatory illness, so as not to interpret this new demographic trend in a purely negative light.

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

The move towards 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 CAN BE RESPONSIBLE FOR UNEXPECTED DEMOGRAPHIC TRENDS

While major shifts in the population should have direct affect on the incidence of environmental pollutant-related illness, 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 pollutants 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 will grow faster with age than before. 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 quite 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, consequently leading to a lowered life expectancy figure 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 rate 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.

For instance, tighter pollution controls, if it is assumed such controls will have their greatest effect on cancer incidences, could eventually lead to an increase either in cariovascular deaths or to the rise of a major new group of mortalities. Decreased smoking would also tend to have the same result.

An interesting point of speculation is the indirect health effects of mandatory retirement ages. The removal of workers from hostile (heavily polluted) occupation environments as they reach ages of progressively increasing susceptibility might be an indirect health boon.

Extraordinarily 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 became, *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. HOW TO MODEL HETEROGENEITY

Heterogeneity models use two sets of assumptions. One of them 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. Recently, one of the most widely used has been the proportional hazard model. In this model, the hazard rate $h(t,z)$ can be described in terms of the product of the two function: $\mu(t)$, which depends only on time at age t, called the underlying hazard and $g(z)$, which depends only on the influential

variable:

$$h(t,z) = \mu(t)*g(z) \quad .$$

In Cox (1972) model $g(z)$ takes the form:

$$g(z) = e^{\beta z}$$

where β is an unknown parameter which should be estimated. The observed variable z could specify, for instance, the level of the environmental pollution in some particular area.

Some of the heterogeneity variables are unobserved. The natural question is how can one develop the data processing algorithms in the presence of these hidden heterogeneity factors. The traditional way to solve this problem is simply to ignore this kind of heterogeneity. However, some studies show that ignoring unobserved influential factors in mortality models may lead to biases in parameter estimation (Elbers and Ridder 1982; Gail, Wieand, and Piantadosi 1984; Vaupel and Yashin 1985c).

Thus in cases where estimation precision is important, one should take care to consider unobserved heterogeneity. The manner of treatment depends on the ancillary information about unobserved variables.

9. MODELS OF UNOBSERVED BIOLOGICALLY STIPULATED HETEROGENEITY

Vaupel, Manton and Stallard (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:

$$h(t,z) = z^* \mu(t) \quad .$$

The inherent factors that influence mortality may be modeled in terms of heterogeneity variables that do not change with age. This variable is often called frailty in proportional hazard models. Calculations show that for arbitrary distribution of z the changes of average frailty in the population z_t have some regularity conditions.

More precisely average frailty in the cohort decreases as the cohort ages. Such changes of average frailty may produce unexpected results in population dynamics. Among the facts that may be regarded as artifacts of heterogeneity one can find that individuals age faster than one can observe, the success of medical

programs may have negative consequences on mortality, and life expectancy, convergence, and crossovers of the mortality curves for some groups of individuals in the population can be also the artifacts of heterogeneity.

The widely used distribution of frailty is Gamma distribution. It takes the following density function:

$$f(z) = \frac{\lambda^k z^{k-1} e^{-\lambda z}}{\Gamma(k)} \quad .$$

The straightforward calculation show that for observed mortality $\mu(t)$ in this case the following expression is true:

$$\bar{\mu}(t) = \frac{k\,\mu(t)}{\lambda + \int_0^t \mu(s)ds} \quad .$$

If $\bar{z}_0$ is equal to 1 then the formula for $\mu(t)$ can be simplified to:

$$\bar{\mu}(t) = \frac{\mu(t)}{1 + r^2 \int_0^t \mu(s)ds} \quad .$$

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.

The influence of a wide variety of processes on human mortality leads to the models of changing or acquired heterogeneity. These models can be analyzed through the framework of the following formal scheme.

10. MODELING OF ACQUIRED HETEROGENEITY

Let us assume that the duration of life for any individual in the cohort depends on multidimensional process z_t. The trajectories of the processes differ from individual to individual. The components may be the concentration of pollutants in the local environment, social and economic differences, behavioral factors, etc.. The most appropriate way to describe this variety is to use a stochastic process model (Yashin, Manton, Vaupel 1985).

The dependence of the hazard rate on the values of the process z_t may be simplified in terms of some parametric function:

$$\mu(t,z_t) = f(t,\alpha,z_t)$$

where α is the vector of unknown parameters. The functional form of (t,α,z_t) is determined from special studies. There are results that show that for some particular continuously distributed influential process this function is the quadratic form of z_t. For finite state continuous time stochastic processes the dependence $\mu(t,z_t)$ on z_t can be an arbitrary function. The fundamental result of the heterogeneity analysis is to establish the correspondence between observed mortality $\mu(t)$ and mortality $\mu(t,z_t)$ conditional on process z_t. This relationship is:

$$\bar{\mu}(t,\alpha) = E(\mu(t,z_t) \mid T > t)$$

where T is the death time specified as a positive random variable.

Note that the dependence $\mu(t,z_t)$ on unknown parameters produces the dependence $\mu(t,\alpha)$ on these parameters. If the available data are about the death time of N individuals $(t_1,t_2,\ldots,t_N)$ then one can form the likelihood function:

$$L(t_1,\ldots,t_N) = \prod_{i=1}^{N} \mu(t_i,\alpha) e^{-\int_0^{t_i} \bar{\mu}(s,\alpha)ds}$$

and use it for parameter estimation.

If heterogeneous variation is a process which changes in steps over time with a finite number of states and a matrix of transition coefficients $q_{ij}(t,\alpha)$, then the formula for $\bar{\mu}(t,\alpha)$ is as follows:

$$\bar{\mu}(t,\alpha) = \sum_i \mu(t,i)\, \Pi_i(t)$$

where $\pi_j(t)$ are the solutions of the following ordinary nonlinear differential equations:

$$\frac{d\pi_j(t)}{dt} = \sum_i q_{ij}(t,\alpha)\pi_i(t) + \pi_j(t)\left[\sum_{i=1}^{N} \mu(t,i)\pi_i(t) - \mu(t,j)\right]$$

where N is the number of states.

Very often data about death times contains information about cause of death. The influence of the process z_t on the cause-specific mortalities $f_i(t,z_t)$ creates the situation where different causes of death become dependent. Traditional models of competing risk use the independence assumption which does not hold true in models of heterogeneity with competing risks.

It turns out that even in this case one can develop an approach which allows one to organize data-processing algorithms using the maximum likelihood approach. If $\lambda_i(t,z_t) = \varphi_i(t,z_t,\alpha)$ are the functional parametric forms of the conditional cause-specific mortality then for $\bar{\lambda}_i(t,\alpha)$ we can derive the formula:

$$\bar{\lambda}_i(t,\alpha) = E(\lambda_i(t,.z_t,\alpha) \mid T > t)$$

In the case when data specifies the death times and causes of death $t_i^{i_1}, t_2^{i_2}, \ldots$ the likelihood function is:

$$L(t_1^{i_1}, t_2^{i_2}, \ldots, t_N^{i_N}) = \prod_{k=1}^{m} \bar{\lambda}_{i_k}(t_k^{i_k},\alpha) e^{-\sum_j \int_0^{t_k^{i_k}} \bar{\lambda}_j(s,\alpha)ds}$$

when i_k is cause of death for k-th individual and m is the number of causes of death.

Yashin, Manton, and Vaupel (1985) considered stochastic process models of mortality and aging in the presence of heterogeneity that can change over time. Continuous time and continuous state stochastic processes were 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, Manton, and Stallard (1985a,b).

11. CONCLUSION

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 recognized 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 and mortality. To help predict the importance of such changes, heterogeneity can be modelled in a variety of ways to give greater insight into the effect of changes among different cohorts.

Methods developed for capturing unobserved heterogeneity show ways of incorporating ancillary information into the models. Combining these models with measurement data provides an opportunity to develop numerical procedures for parameter estimation as well as identification of the model.

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