Air Toxics Regulatory Issues Facing Urban Settings

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Biomarker research does not exist in isolation. Its usefulness can only be realized when it is translated into prevention strategies to protect public health. In the context of air toxics, these prevention strategies begin with the development of regulatory standards derived from risk assessment schemes. The Clean Air Act Amendments of 1990 list 189 air toxics, including many volatile organics, metals, and pesticides. The National Institute of Environmental Health Sciences (NIEHS), through its affiliation with the National Toxicology Program, has generated toxicity and carcinogenicity data on more than 100 of these air toxics. The NIEHS extramural and intramural research portfolios support a variety of projects that develop and validate biomarkers for use in environmental health science and risk assessment. Biomarkers have a tremendous potential in the areas of regulating air toxics and protecting public health. Risk assessors need data provided by biomarkers of exposure, biomarkers of dose/pharmacokinetics, biomarkers of susceptibility or individual variability, and biomarkers of effects. The greatest benefit would be realized if biomarkers could be employed in four areas of primary and secondary prevention. The first is the use of biomarkers to enhance extrapolation of animal data to human exposure situations in establishing risk standards. The second is the use of biomarkers that assess noncancer, as well as cancer, end points. Important health end points include pulmonary dysfunction, immunotoxicity, and neurotoxicity. Third, biomarkers that serve as early warning signs to detect intermediate effects would enhance our ability to design timely and cost-effective intervention strategies. Finally, biomarkers used to evaluate the effectiveness of intervention strategies, both in clinical and regulatory settings, would enable us to ensure that programs designed to protect public health do, in fact, achieve the desired outcome. — Environ Health Perspect 104(Suppl 5):857–860 (1996)

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Introduction

Modern technology has greatly enhanced our quality of life. Pesticides have expanded our agricultural capacity, transportation systems allow us tremendous mobility, and plastics have transformed our homes and workplace. The technologies and industries that have allowed this progress, however, have also led to some unwanted and unintended side effects. One such side effect is the deterioration of the air we breathe.

Environmental ethics have changed since the early days of the Industrial Revolution, when certain detrimental changes in the quality of the environment were accepted as unavoidable costs of progress. Today, we realize that the relationship between humans and the environment is both dynamic and fragile and that our lives depend on the health of the environment. This realization has led to increased contentiousness between proponents of development and those for conservation, and between issues of industrialization and of environmental public health. In the context of air pollution, these difficulties and conflicts arise in large measure from two important facts.

The first of these is that there are gaps and uncertainties both in the databases used to define adverse environmental effects and in the extrapolation techniques used to generate risk estimates based on laboratory data. Filling these gaps and resolving these uncertainties is paramount if we are to more rationally manage the economic benefits to be derived from modern technology in ways that preserve quality of life and sustainability of that quality into the future.

The second cause for conflict is that the adverse effects of air pollution are not equitably distributed. Air pollution moves, so an area can suffer from air pollution problems not of its own creation. Additionally, not everyone is equally susceptible to health effects related to air pollution. The elderly, the very young, the poor, and those in poor health can be more vulnerable to adverse effects related to poor air quality. For these reasons, resolving air pollution problems is more amenable to group or regulatory action than to individual action.

Regulatory History

In the United States, the first attempts to control air quality in urban settings date to the 1970 Clean Air Act Amendments. While air pollution was the first federal air quality law, the Air Pollution Control Act of 1955, the federal role was to generate information and support research rather than to regulate. The political environment slowly changed, however, and regulation of air quality as we know it began in 1970 with the establishment of the Environmental Protection Agency (U.S. EPA) and the 1970 Clean Air Act Amendments, which created a stronger regulatory role for the federal government (1).

The 1970 Clean Air Act Amendments established two types of air pollutants for regulatory purposes. The first of these were the criteria air pollutants that had been

*The Clean Air Act and its amendments focus on outdoor air quality. There is no single act covering indoor air quality, although the Occupational Safety and Health Administration addresses indoor air quality issues in occupational settings, and the U.S. EPA conducts risk assessments on air quality issues such as radon and second-hand smoke. Indoor air quality is of increasing concern; the U.S. Department of Labor estimates that up to 30% of U.S. office buildings have indoor air quality problems (2). Several of the air toxics listed in the 1990 Clean Air Act Amendments, such as formaldehyde and asbestos, are implicated in indoor air quality problems.
named in previous amendments. These six pollutants—ozone, carbon monoxide, particulate matter, sulfur dioxide, nitrogen dioxide, and lead—are common throughout the United States. National Ambient Air Quality Standards have been set for each and serve as a basis for determining whether or not an area is in compliance with the nation’s air quality program. The criteria air pollutants are widely distributed throughout the country and are a demonstrated hazard both to human health and to the health of the ecosystem. It is because of this broad distribution that they were selected for use as national measures of air quality. There are other air pollutants, however, that are also hazardous to health and to the environment, although their composition tends to be more regional rather than reflective of the country as a whole. These hazardous air pollutants, or air toxics, can be released from small stationary sources such as dry cleaners and auto paint shops, from large stationary sources such as chemical factories, and from mobile sources such as automobile exhaust. The 1970 Clean Air Act Amendments authorized the U.S. EPA to regulate air toxics and specifically called for action on mercury, beryllium, and asbestos.

In the intervening 20 years between 1970 and the 1990 Clean Air Act Amendments, regulation under the criteria air pollutant program helped achieve the improvement in air quality that we enjoy today, although ozone, carbon monoxide, and particulate matter are still widespread problems. The air toxics program, however, was less successful. Standards were set on only seven of the many potential air toxics: arsenic, asbestos, benzene, beryllium, mercury, radionuclides, and vinyl chloride. It was this failure to regulate the bulk of air toxics that persuaded Congress to try a different approach in 1990.

Under the 1990 Clean Air Act Amendments, the Congress listed 189 substances presumed to merit the label “air toxic.” About half of these substances are volatile organics, including benzene, carbon tetrachloride, butadiene, tetra-chloroethylene, and xylene. Various metals also figure prominently in the list as do a number of pesticides. Although the list is subject to change, to date the only changes made are that hydrogen sulfide has been removed from the list and the glycol ethers have been more completely listed by CAS number. The current list of air toxics is given in Table 1.

In these amendments, the Congress directed the U.S. EPA to regulate based on what was technologically possible. In the terminology of the 1990 Clean Air Act Amendments, industry should use the maximum achievable control technology (MACT). The 1990 Clean Air Act Amendments acknowledge, however, that employment of the “best available technology” might still present residual risk to exposed populations or subpopulations. Therefore, the U.S. EPA, after identifying the categories of air toxic emissions and setting MACT standards for each category, must examine the need for additional standards that address the issue of residual risk. For carcinogens the acceptable risk level would be $10^{-6}$.

**Current Database**

Animal bioassays remain the backbone of most risk assessment determinations. Probably the most extensive database of high-quality animal testing in the world is that generated by the National Toxicology Program (NTP). The NTP is a unique national resource because not only are studies conducted in a consistent and tightly controlled manner, but all data material, including slides, blocks, and wet tissues, are archived and available for further examination. Additionally, beginning in 1987, the NTP began saving tissue from all animal tumors found in chronic bioassays. This material is frozen and archived so that, as important oncogenes and tumor-suppressor genes are identified, these tissues can be recovered and data results reinterpreted in light of new information.

The NTP also recognizes the value of mechanistic data. In the past, chemical disposition and pharmacokinetic data were generated on a number of studies under test. This effort has now become routine, and the majority of 2-year bioassays include pharmacokinetic, mechanistic, and dosimetric studies.

Of the 189 air toxics listed in the 1990 Clean Air Act Amendments, more than 100 have been studied by the NTP. As shown in Table 2, about 70% of the compounds studied in short-term tests were also studied in long-term, chronic tests; 23% of those studied in chronic assays were conducted by the inhalation route of exposure. Chemical disposition information has been generated on 61 compounds listed as air toxics and NTP-conducted genetic toxicity assay on 195 air toxic compounds. (The number exceeds the list of 189 air toxics because the 1990 Clean Air Act Amendments employed categories of compounds, such as the glycol ethers, which incorporate many separate compounds for study.) Ninety-two air toxic compounds have been studied in some type of organ system assay. These assays include measures of teratology, reproductive function, neurotoxicity, and immunotoxicity. Clearly the NTP database makes a significant contribution to our knowledge of air toxics and will figure prominently in future risk assessment determinations.

**Potential of Biomarkers in Risk Assessment**

As mentioned in the Introduction, conflicts over managing air quality arise not only from gaps in the database, but also from uncertainties inherent in extrapolating from existing data sets to actual exposure situations. Moving toward a health-based regulatory approach for air toxics will require a tremendous improvement in the science of toxicology. It will require better ability to assess exposures and an understanding of mechanisms of disease causation, of pharmacokinetics, of dose-response relationships, and of individual differences in susceptibility. The National Academy of Sciences, in its report assessing current risk assessment methodology, envisioned moving toward a regulatory environment in which biologic measures that reflect human exposure situations will replace default assumptions that ignore human variability or introduce conservative measures to avoid it. Enhancing our ability to achieve this worthwhile goal clearly resides within the purview of biomarker research. The literature already contains promising results on the potential of this technology in air toxics research.

For example, Perera et al. (7) used biologic indicators to establish a link between environmental air pollution and molecular and genetic damage in humans. These studies compared populations in areas of Poland with highly polluted air with those living in relatively unpolluted rural areas. They found that living in areas of highly polluted air was associated with significant increases in carcinogen–DNA adducts, sister chromatid exchange, chromosomal aberrations, and rasi gene overexpression.

Other investigators have been attempting to understand DNA–protein cross-linking by metals, the role of this cross-linking in carcinogenesis and toxicity, and the potential of cross-linking as a biomarker of exposure and effect. It is known that chromium and nickel induce DNA–protein cross-links.
Table 1. Air Toxics, 1990 Clean Air Act.

| CAS no. | Chemical name                                      | CAS no. | Chemical name                                      | CAS no. | Chemical name                                      |
|---------|----------------------------------------------------|---------|----------------------------------------------------|---------|----------------------------------------------------|
| 75070   | Acetaldehyde                                       | 119937  | 3,3'-Dimethylbenzidine                             | 82688   | Pentachloronitromethane (quinolobenzene)           |
| 60355   | Acetamide                                          | 79447   | Dimethylcarbamoyl chloride                         | 87885   | Pentachlorophenol                                  |
| 75658   | Acetanilide                                        | 68122   | Dimethyl formamide                                 | 108552  | Phenol                                             |
| 98682   | Acetoephene                                        | 57147   | 1,1-Dimethyldiazene                                | 108630  | p-Phenlenediamine                                 |
| 53863   | 2-Acetylaminofluorene                              | 13113   | Dimethylphenylaldehyde                             | 75445   | Phosgene                                           |
| 107028  | Acrolein                                           | 77781   | Dimethyl sulfate                                   | 7723140 | Phosphorus                                         |
| 79601   | Acrylamide                                         | 534521  | 4,6-Dinitro-o-cresol, and salts                    | 7803512 | Phosphine                                          |
| 79107   | Acrylic acid                                       | 51285   | 2,4-Dinitrophenol                                  | 1120714 | 1,3-Propane sultone                               |
| 107131  | Acrylonitrile                                      | 121142  | 2,4-Dinitrotoluene                                 | 85449   | Phthalic anhydride                                 |
| 107051  | Allyl chloride                                     | 123911  | 1,4-Diaxone (1,4-diethylenediol oxide)             | 1336363 | Polychlorinated biphenyls (Aroclors)               |
| 92671   | 4-Aminobiphenyl                                   | 122867  | 1,2-Diphenylethydrine                              | 110947  | 1,3-Propane sultone                               |
| 62533   | Aniline                                            | 106898  | Eryphothloroethylene (1-chloro-2,3-)               | 57578   | p-Propiolactone                                    |
| 99040   | o-Aminisidine                                      | 109687  | eryphothloroethylene (epoxypropane)                | 123386  | Propionaldehyde                                    |
| 1332214 | Asbestos                                           | 106887  | 1,2-Epoxybutane                                    | 114261  | Propoxur (banygon)                                |
| 71432   | Benzene (including benzene from gasolin)           | 140885  | Ethyl acrylate                                     | 78875   | Propylene dichloro (1,2-dichloro-propane)          |
| 92875   | Benzidine                                          | 51796   | Ethyl carbamate (urethane)                         | 75569   | Propylene oxide                                    |
| 75150   | Carbon disulfide                                   | 87883   | Hexachlorobutadiene                                | 95807   | 2,4-Toluene diame                                  |
| 56226   | Carbon tetrachloride                               | 77474   | Hexachlorocyclopentadiene                          | 584894  | 2,4-Toluene disocacylate                           |
| 46351   | Carbonyl sulfide                                   | 67721   | Hexachloroethane                                   | 85354   | α-Toluidine                                        |
| 120809  | Catchaline                                         | 822060  | Hexamethylene-1,6-disocacylate                     | 8001352 | Tetraphene (chlorinated camphene)                  |
| 133904  | Chlorobenzene                                      | 680319  | Hexamethoxyporphoramide                            | 120821  | 1,2,4-Trichlorobenzene                            |
| 57740   | Chloride                                           | 110543  | Hexane                                             | 79005   | 1,1,1-Trichloroethane                             |
| 7782506 | Chlorine                                           | 302012  | Hydrazine                                          | 79016   | Trichloroethylene                                  |
| 79119   | Chloroacetic acid                                  | 7647010 | Hydrochloric acid                                  | 959540  | 2,4,5-Trichlorophenol                              |
| 532274  | 2-Chloroacetoephene                                | 7664933 | Hydrogen fluoride (hydrofluoric acid)               | 800620  | 2,4,6-Trichlorophenol                              |
| 106897  | Chlorobenzene                                      | 123319  | Hydroquinone                                       | 1214480 | Triethylamine                                      |
| 510156  | Chlorobenzilate                                    | 78591   | Isophorone                                         | 15820980| Trifluorane                                        |
| 67663   | Chloroform                                         | 58699   | Lindane (all isomers)                              | 5408410 | 2,2,4-Trimethylpentane                            |
| 107302  | Chloromethyl methyl ether                          | 108316  | Maleic anhydride                                   | 1080540 | Vinyl acetate                                      |
| 126938  | Chloroform                                         | 67641   | Methanol                                           | 5936020 | Vinyl chloride                                     |
| 3139773 | Cresol/cresylic acid (isomers and mixture)         | 72435   | Methoxychlor                                        | 750140  | Vinyl chloride                                     |
| 95487   | o-Cresol                                           | 74839   | Methyl bromide (bromomethane)                      | 75540   | Vinyliden chloride (1,1-dichloroethylene)          |
| 106549  | m-Cresol                                           | 71556   | Methyl chloroform (1,1,1-trichloroethane)          | 13302070| Xylenes (isomers and mixtures)                     |
| 98828   | Cumene                                             | 78933   | Methyl ethyl ketone (2-butane)                     | 1083300 | m-Xylene                                           |
| 94757   | 2,4-Dichlorophenoxyacetic acid, salts and esters   | 60344   | Methyl hydrazole                                   | 10842200| p-Xylene                                           |
| 354704  | 1,1-Dichloro-2,2-bis(p-chlorophenyl) ethylene      | 108101  | Methyl isobutyl ketone (hexene)                    | 0       | Antimony compounds                                 |
| 334863  | Diazomethane                                       | 80629   | Methyl methacrylate                                | 0       | Beryllium compounds                                |
| 132649  | Dibenzoferans                                      | 163444  | Methyl tert-butyll ether                           | 0       | Cadmium compounds                                  |
| 96619   | Benzo(c)-chloropropane                             | 101144  | Methylglyoxal (2-chloroaniline)                     | 0       | Chromium compounds                                 |
| 84742   | Dibutylylaldehyde                                  | 75992   | Methylene chloride (dichloromethane)               | 0       | Cobalt compounds                                  |
| 108647  | 1,4-Dichlorobenzene                                | 101688  | Methylene diphenyl disocacylate                    | 0       | Coke oven emissions                                |
| 91941   | 3,3-Dichlorobenzidine                              | 101779  | Methylene-2,4-dimethylalilin                       | 0       | Cyanide compounds                                  |
| 111444  | Dichloroethyl ether (bis[2]-chloroethyl)ether      | 941203  | Naphthalene                                        | 0       | Glycol ethers                                      |
| 542765  | 1,3-Dichloropropene                                | 92553   | Nitrobenzene                                       | 0       | Lead compounds                                     |
| 62373   | Chloroform                                         | 100027  | Nitrophenol                                        | 0       | Manganeus compounds                                |
| 111422  | Diethanolamine                                     | 79496   | Nitrophenol                                        | 0       | Mercury compounds                                  |
| 12169   | N,N-Diethylaniline (N,N-dimethylaniline)            | 684935  | N-Nitroso-N-methylurea                             | 0       | Fine mineral fibers                                |
| 64675   | Diethyl sulfate                                    | 62759   | N-Nitrosodiethylamine                              | 0       | Nickel compounds                                   |
| 119904  | 3,3-Dimethoxybenzidine                             | 59892   | N-Nitrosomopholine                                 | 0       | Polycolactic organic matter                        |
| 60117   | Dimethylnitromethane                               | 56382   | Parathion                                          | 0       | Radiationclides (including radon)                 |
|         |                                                   |         |                                                   | 0       | Selenium compounds                                 |
Table 2. NTP studies of the Clean Air Act air toxics.

| Route of administration | Chemical disposition | Genetic toxicity | Organ systems toxicity |
|--------------------------|----------------------|------------------|-----------------------|
| Inhalation               |                      |                  |                       |
| Subchronic*             | 12                   | 61               | 92                    |
| Chronic                 | 20                   |                  |                       |
| Other                    | 23                   |                  |                       |
| Subchronic*             | 66                   |                  |                       |
| Chronic                 |                      |                  |                       |

*Limited to chemicals that did not have subsequent chronic studies performed.

and are one of the primary lesions induced in cells exposed to these metals. Costa et al. (8,9) have evaluated the feasibility of using a DNA–protein cross-link assay in peripheral white blood cells to detect human exposure to both chromium and nickel compounds in occupational settings. Their results showed an elevation in this biomarker related to chromium and nickel exposures, verifying its usefulness as a biomarker of exposure. If one presumes that target tissues such as the lung also have these types of lesions, then this assay might also serve as an early warning of potential disease development.

These are but two examples of some of the work emerging in the field of biomarker research. The availability of these and other biomarkers will help measure individual exposures, define mechanisms and pathways in disease causation and establish whether these pathways are common to both animals and humans.

Future Use of Biomarkers in Risk Assessment

The value of biomarker research can only be realized when it is used in prevention and intervention strategies that protect public health. Focusing on human health needs leads to four overarching areas of biomarker use.

First there is a need for biomarkers that can be used in the risk assessment arena to enhance extrapolation from animal data to human exposure situations. These would be biomarkers that reveal common mechanistic pathways relevant to toxicity in both humans and animals and could ideally be an integrated measure of events occurring over time. Biomarkers that can account for individual variability or susceptibility would also be useful components for extrapolation schemes.

Second, we must remember that human health is affected by many different diseases, of which cancer is only one. Important disease end points to consider include pulmonary dysfunction, immune dysfunction, and birth defects. Biomarkers for these and other noncancer end points will be a critical need in the future.

Third, human health can best be protected when intervention and treatment strategies are employed prior to clinical expression of a disease. Developing biomarkers that serve as early warning signs to detect intermediate effects would greatly enhance our ability to design successful, cost-effective public health strategies. These biomarkers could be chemical, pathological, or functional in nature.

Lastly, biomarkers could be employed in an evaluative capacity. They could assess the efficacy of prevention and intervention strategies, both in clinical and regulatory settings. This latter evaluative component could help ensure that dollars spent protecting public health do, in fact, achieve the desired outcome. This results- or outcome-oriented use of biomarkers, if successful, would greatly enhance regulatory agencies’ ability to assess the relevance of their programs.

This view of the future must be tempered with an understanding of the ethical considerations of biomarker use. Biomarkers of exposure, of internal dose, and of biologically effective doses will be of tremendous benefit in regulating human exposures and protecting public health. More problematic, however, are biomarkers that indicate altered structure or function, the presence of clinical disease, or enhanced susceptibility to toxic compounds. Information from these biomarkers could potentially be used to deny access to jobs or insurance. The social and ethical problems surrounding the use of biomarkers and susceptibility information need to be anticipated and rational schemes devised to circumvent misuse of this promising technology.

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