Some Considerations Concerning Multimedia–Multipollutant Risk Assessment Methodology: Use of Epidemiologic Data for Non-Cancer Risk Assessment in Russia

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The highly industrialized small town of Verkhnyaya Pyshma (in the Urals region of Russia) was chosen as the site of a multimedia–multipollutant risk assessment using the U.S. Environmental Protection Agency methodology. The assessment was based on routine environmental pollution monitoring data for ambient air, soils, drinking water, and food, and the international environmental epidemiology literature. Using an *a priori* set of the preliminary health-based criteria, we selected nine pollutants for risk assessment: total suspended particles (TSP), sulfur dioxide, nitrogen dioxide, benzo(a)pyrene (BaP), ammonia arsenic, copper, cadmium, and lead. We used dose–response functions derived from epidemiologic studies to assess individual and population risks for TSP, SO_2, NO_2, As, Cd, and Pb. We assessed both cancer (for BaP, As, and Cd) and non-cancer (for all the chosen pollutants but BaP) responses, but in this paper we discuss only the assessments of noncarcinogenic risks due to TSP, SO_2, NO_2, Pb, and Cd as examples of how the quantitative estimates of health effects can be produced by using a risk function approach. We also schematically present a modified conceptual model of multimedia–multipollutant risk assessment taking into account the experience gained with this study. *Key words*: industrial pollution, population health, risk assessment, Russia. *Environ Health Perspect* 109:7–13 (2001). [Online 27 November 2000]
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Environmental health risk assessment, or health impact assessment as it is coming to be known, is increasingly being used in Western countries to provide information for developing environmental health policy and to assist decision makers by providing estimates of the health effects associated with local environmental exposures and their potential distribution in the population. This information can be used to evaluate alternate choices with respect to environmental action. Epidemiologists have been increasingly involved with this method, both in terms of designing and reporting the studies from which risk functions and underlying population distribution functions can be derived and in terms of conducting the health risk assessment themselves. To emphasize the interest of epidemiologists in this growing field, it should be noted that two professional associations, the International Society of Environmental Epidemiology (ISEE) and the American College of Epidemiology, focused on health risk assessment and policy issues at their annual meetings in 1999.

In the past decade, a variety of efforts have also been undertaken to extend the use of these techniques to developing countries and to countries with economies in transition. In many of these countries, where risk assessment has not previously been an analytical method of choice, the local information necessary to perform risk analysis is not always available. Furthermore, the conceptual approaches underlying these methods may be incompatible or even contradictory to more traditional local methods of environmental health management. Nonetheless, risk assessments can be and have been performed successfully by using a combination of local information and data from the international literature and by tailoring the science policy judgment to local sensibilities. Decision makers receive valuable information about the relative magnitude of risks, sources of risk, and the subpopulations most at risk from the integrated risk assessment/traditional health management approach.

Recent work in Russia provides several practical examples of the types of issues that can be encountered when a health impact assessment is conducted in a country where this technique represents some departure from previous methods of collecting and using information. In November 1997, two government agencies of the Russian Federation—the State Sanitary and Epidemiological Surveillance (SanEpid) and the State Environment Protection Agencies—issued a mutual decree that provided a basis for the use of environmental health risk assessment in priority setting and decision making

in Russia. Since that time, a number of projects have moved forward, providing models for further work of this type in Russia. We implemented the first project dealing with multimedia–multipollutant risk assessment based on routine environmental pollution monitoring data in the city of Verkhnyaya Pyshma; our study was within the framework of the Project on Environmental Management in the Russian Federation, which was sponsored by the World Bank.

Verkhnyaya (Upper) Pyshma is a highly industrialized small city with a population of approximately 53,000 (Table 1) located in the Sverdlovsk Oblast (the Urals region) of the Russian Federation. The general negative demographic trend in the Russian Federation is more marked in the Sverdlovsk Oblast as a whole, but in this city the trend is even more pronounced: for example, in 1998 the differences between the birth rate and mortality rate per 1,000 population were –5.3, –6.5, and –7.1, respectively.

There are 74 registered industrial enterprises in the city, but 3 predominate in terms of industrial emissions: the Ural Electrolytic Copper Refinery (UECR), the Ural Plant of Rare Metals, and the Ural Plant of Chemical Reagents (UPCR). Atmospheric emissions have decreased sharply since 1992 because of the decreases in production, so the concentrations of air pollutants registered in the 1990s were not especially high (Table 2).

Historically, levels were much higher; however, environmental pollution remains a concern in the city because of past practices and because of the potential for increased emissions with future economic growth. The contamination of soil (and dust) with toxic

metals over a long period from their sedimentation from the polluted atmosphere not only provides stable evidence of this past pollution but is an important source of direct and food-mediated exposure of the population (Table 3).

The purpose of the risk assessment was to inform local decision makers about the relative importance of existing levels of pollution in their town and to recommend local actions to more thoroughly investigate and address the most important environmental threats to public health. Moreover, we planned to evaluate the applicability of risk assessment methodology in the Russian context and to provide Russian specialists with some practical experience for the further use of this methodology.

Methods

The Verkhnyaya Pyshma risk assessment generally followed the risk assessment methodology used by the U.S. Environmental Protection Agency (U.S. EPA). The U.S. EPA methodology for conducting a risk assessment specifies four steps: hazard identification, exposure assessment, dose–response assessment, and risk characterization. Each step in this risk assessment involved both the collection of scientific information on local conditions and important science policy judgments regarding the types of hazards and exposures to assess, the level of conservatism to use in dose–response functions, and the kinds of risk metrics to report to decision makers. These science policy decisions were made in the context of existing well-established and officially recognized methods of environmental health evaluation and decision making in Russia.

We developed a conceptual model (Figure 1) based on models of risk assessment proposed by other authors (1–8) and on our own experience. Our model, like some others (3,8), emphasizes the necessity of feedback between the above-mentioned steps rather than presenting risk assessment as a straight-line process (a more common approach). More specifically, the results of earlier steps in the assessment are reevaluated with the completion of each succeeding step. Certain features of this model are new, and reflect some adjustment of the U.S. EPA methodology to Russian conditions and traditions.

Table 1. The age and sex distribution of the Verkhnyaya Pyshma population (1996).

Age (years)	Sex	
	Male	Female
0–5	2,860	2,870
6–15	4,253	4,167
16–59	15,169	16,663
≥ 60	2,183	4,918
All ages	24,465	26,618

Review of Available Environmental Contamination and Exposure Data

The first step of the Verkhnyaya Pyshma assessment was to review available environmental data to determine what contaminants were present in the city, in which media, and at what concentrations. Environmental contaminant and health data are being collected by city level and oblast level offices of the State SanEpid, the Ministry of Public Health, and the State Hydrological and Meteorological Service (Hydromet). Among other duties, these agencies are responsible for the routine collection of data on environmental concentrations of pollutants in air, surface water, drinking water, soils, and food. The regional government statistical service collects information on dietary intakes that can be used for exposure assessment.

Air. Data on air pollution were derived from the daily monitoring of air pollutants at three monitoring stations. Two of these stations are operated by industry, and the third is operated by the State SanEpid Center of the City of Verkhnyaya Pyshma. The SanEpid monitoring station is near the station operated by the UECR, and the third station is operated by the UPCR. In this study, we refer to the area near the UECR and the SanEpid stations as Area I, and the area near the UPCR as Area II. Because the UECR and UPCR monitoring stations are located in different areas of the city and these enterprises represent very different industrial processes, we attempted to characterize average exposure through air and soil separately for people residing in each of the two areas. However, it was difficult to draw a distinct boundary between these areas, and too much uncertainty was involved in assigning particular subpopulations to either area; thus estimated exposures (and assessed risks) were, as a rule, averaged across the city.

Water. Drinking water concentrations of both chemical and microbiologic pollutants in Verkhnyaya Pyshma are routinely monitored. There are three centralized drinking water supply systems in the city that draw water from various aquifers. However, because the systems are interconnected, exposure to pollutants can only be assessed for the population of the city as a whole. The levels of metal pollutants found in the drinking water were comparable to those seen in a nearby community of Sredneuralsk, which had far less soil pollution by metals. This suggests that the deep-level aquifers from which the public water supply is drawn are relatively unaffected by the contamination of surface soil by metals.

Table 2. Concentrations (mg/m^3) of some ambient air pollutants in Verkhnyaya Pyshma (from routine monitoring in 1996).

Pollutant	Annual average	Range
Total suspended particles	0.124	0.027–0.584
Sulfur dioxide	0.027	0.001–0.097
Sulfuric acid	0.007	0.003–0.060
Nitrogen dioxide	0.021	0.010–0.126
Ammonia	0.063	0.010–0.370
Hydrocloric acid	0.131	0.016–0.760
Phenol	0.007	0.002–0.037
Formaldehyde	0.002	0 – 0.060
Benzo(*a*)pyrene	4×10^{-7}	$1 \times 10^{-7} - 2 \times 10^{-6}$
Lead	2.9×10^{-5}	$0 - 3.0 \times 10^{-3}$
Cadmium	3×10^{-6}	$0 - 1.5 \times 10^{-4}$
Copper	1.3×10^{-4}	$4 \times 10^{-5} - 1.2 \times 10^{-3}$
Zinc	1×10^{-4}	$0 - 7 \times 10^{-4}$
Vanadium	4×10^{-5}	$1 \times 10^{-5} - 5 \times 10^{-5}$
Nickel	8×10^{-5}	$1 \times 10^{-5} - 1.3 \times 10^{-4}$
Cobalt	5×10^{-5}	$1 \times 10^{-5} - 8 \times 10^{-5}$

Table 3. Concentrations (mg/kg) of some metals in soils of Verkhnyaya Pyshma and in vegetables grown in private gardens close to town.

Metal	Soil		Locally produced vegetables (average)[a]		
	Concentration (range)	Background value[b]	Potato	Carrot	Beet
Copper	539.2–7708.2	18.1	0.97	0.66	1.58
Lead	17.6–168.8	19.0	0.23	0.24	0.26
Zinc	56.8–269.7	68.8	2.60	2.30	4.32
Cadmium	0.006–16.5	0.44	0.015	0.012	0.011
Arsenic	ND–12.2	5.85	No data	No data	No data
Nickel	37.3–297.7	75.6	No data	No data	No data

ND, not detected.
[a]These data contrast with levels from other areas of the region; the average lead content of the same vegetables grown near Kushva, a town without significant industrial emissions, was 0.009 mg/kg for potatoes and carrots, and 0.027 mg/kg for beets. [b]Average for four samples taken in forests around the town approximately 3 km from its boundaries.

Food. Levels of pollutants in foods were determined through a series of analyses conducted at the Verkhnyaya Pyshma SanEpid laboratory. The food items analyzed represented typical foods eaten in Verkhnyaya Pyshma and included both locally produced and imported foods. A special analysis of locally grown vegetables showed no excess of various metals over the Russian maximum allowable levels (PDK), the legal reference value for determining food safety. Food intake rates for various food products were taken from Sverdlovsk regional statistics. We assumed that food consumption was similar in varying areas of the city.

Soils. Only limited information from the SanEpid on metal concentrations in soil was available, which we supplemented by a special investigation. The number of analyzed samples per metal ranged from 28 to 37 in Area I and from 9 to 15 in Area II. Although direct exposure from soils was not assessed (except for lead in children), the levels observed enabled risk assessors to understand the extent and sources of contamination in the city. The levels in Area I were considerably higher than those in Area II, and the pattern was similar to that observed in the monitored levels of ambient air pollution.

Selection of Priority Pollutants

Data on environmental contamination in air, soils, water, and food are routinely collected for a large number of contaminants. One of the major practical issues for the resource-limited public health officials in this city was to focus the risk assessment on a smaller, high-priority subset of contaminants. We chose 9 pollutants out of 29 that are routinely monitored for inclusion into the short list for risk assessment: total suspended particles (TSP), nitrogen dioxide, sulfur dioxide, ammonia, benzo(*a*)pyrene, cadmium, lead, arsenic, and copper. The selection of priority pollutants was based on the ratio of the measured environmental concentrations of pollutants in air, water, and soils to the respective PDK values. We included a contaminant if this ratio either exceeded 1.0 in at least one medium (or if the sum of ratios exceeded 1.0 for chemicals of similar toxicologic effect) or was between 0.1 and 1.0 in more than one medium. We also included contaminants in the short list if the potential health effects were of a particularly adverse nature (e.g., carcinogenicity, adverse genetic effects, or adverse effects on the mental development of children).

After we had chosen the priority hazards for identification and further risk assessment, we sought and reevaluated additional information on these (according to the methodology shown in Figure 1). For instance, we analyzed additional samples of soil and vegetables for contamination with lead, cadmium, arsenic, and copper.

Hazard Identification and Dose–Response Assessment

As shown by the model (Figure 1), one of the main goals of the hazard identification stage is the choice of the most important end points for further dose–response assessment. The first official Russian guidelines for risk assessment (prepared by the authors and approved by the Federal SanEpid Department) recommend the following criteria for such a choice:

- Medical and social importance of an effect
- Availability of dose–response data and tolerance (reference) doses or concentrations established or recommended by the U.S. EPA [e.g., in the Integrated Risk Information System (IRIS) database] or by other reputable agencies
- Preference of end points for which epidemiology-based assessments of dose–response relationships can be made over those for which assessments are based on animal experimental data only
- For non-cancer risk estimates, preference was given to end points for which explicit risk characterization in probability values or in number of cases per population exists over those for which the risk level is merely suggested by a ratio of the estimated exposure to the reference one (hazard quotient).

The third of the above criteria needs some explanation. According to Stayner et al. (*9*),

> the U.S. EPA and other U.S. agencies have expressed a preference for using epidemiologic data rather than toxicologic data when possible,

and the situation in Russia is quite similar. Although most Russian PDKs, like similar Western standard values, are based on animal data, the State SanEpid regards them as tentative (although they have the official status of law-enforceable standards) until confirmed with appropriate epidemiologic studies. This philosophy had to be taken into consideration when introducing risk assessment into Russian practice. Also, some human health responses to environmental hazards have no adequate animal experimental counterpart (e.g., an increase in the prevalence of respiratory symptoms and functional impairment caused by irritant gas and particulate exposures, the loss of IQ points due to the exposure of children to lead, and many others). Experimental toxicology cannot provide information for dose–response assessment in these important cases. Consequently, Russian public health environmental decision makers and environmental scientists express a strong preference for the use of epidemiologic evidence when determining hazards and choosing appropriate dose–response information.

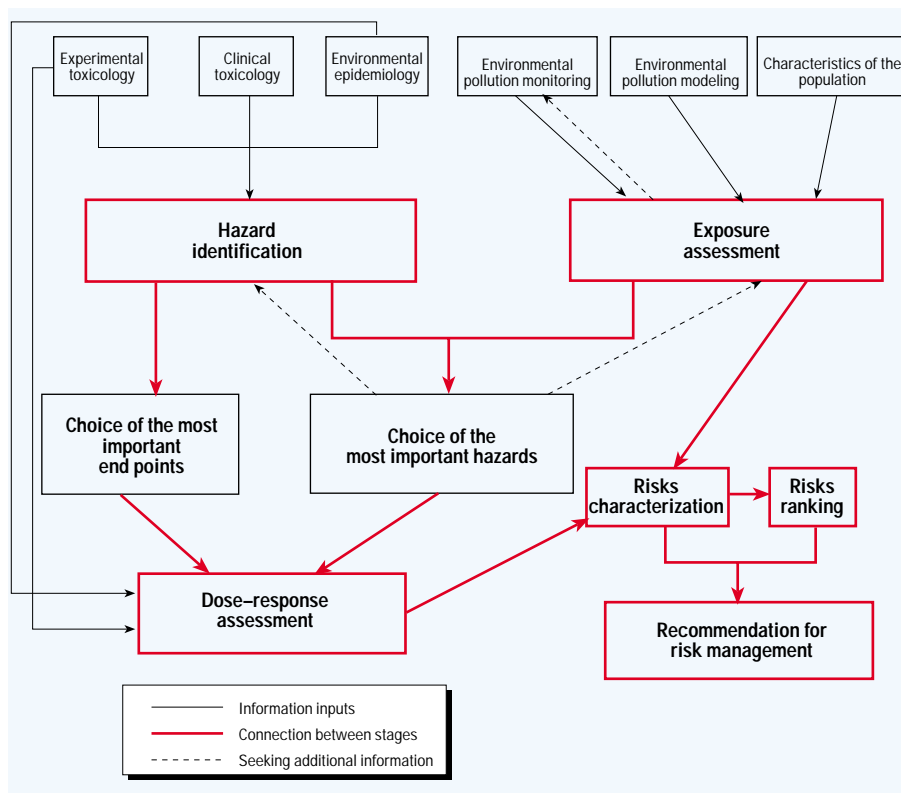Thus, whenever possible in the Verkhnyaya Pyshma case study, we derived

Figure 1. A conceptual model of risk assessment.

dose–response information from epidemiologic studies for all the priority pollutants considered. These data were further supported by available animal toxicologic studies. The review of hazard and dose–response information for the selected contaminants included data from both Russian and American government databases, as well as from the open epidemiologic literature. For a number of the contaminants, we used risk functions drawn from epidemiologic studies or from meta-analyses of such studies. This was the case for TSP, SO_2, NO_2, lead, and cadmium. The risk assessment procedures for this subset of nine priority chemicals are discussed in detail below. We selected these examples because they demonstrate the use of risk functions derived from the epidemiologic literature to estimate non-cancer risks, as well as the evaluation and use of local exposure data for use with these functions.

The results of risk assessment are sensitive to the choice of dose–response functions, and the selection of a function is often an important source of uncertainty in risk assessment in general (10). When applying a risk function derived from the epidemiologic research to exposure–response assessment in this study, we used as our default option a linear extrapolation to exposure levels lower than those for which the function had been based. NO_2 was an exception (see below). In the case of suspended particles, this assumption of linearity is strongly confirmed by Dockery and Pope's analysis of the results of many time–series studies of acute mortality dependence on PM or TSP concentrations (11). They also stressed that no threshold level for this effect has been found in the range of concentrations studied so far. Linearity was used in this study for SO_2 and cadmium as well as a default assumption. In the case of cadmium, we used clinical considerations to define a threshold of its kidney toxicity when analyzing epidemiologic data on internal dose–response relationship.

Although we were careful to avoid double counting when summing the risks (e.g., for TSP and SO_2, which do not act independently) for decision making purposes, the health effects of each specific air pollutant were evaluated separately. This was done because one of the goals of the Verkhnyaya Pyshma case study was to gain an understanding of which pollutants are the most problematic for the town.

TSP

The many adverse health effects of suspended particles depend on chemical composition and size distribution. From the range of health effects associated with exposure to particulates, we chose to evaluate excess total mortality because death is serious and unequivocal, and there was a substantial epidemiologic literature base from which a risk function could be drawn.

Wilson and Spengler (12) reviewed the association of PM_{10} (particulate matter ≤ 10 μm in aerodynamic diameter) with mortality in a number of epidemiologic studies; they concluded that for each increase of 10 μg/m³ in PM_{10}, there is an approximate 1% increase in the daily non-accidental mortality rate. Although the studies forming the basis of this estimate involved acute rather than chronic exposure, we used the relationship to look at increases in the annual mortality rate, based on the assumption that the exposure occurs daily over long periods of time.

Although only TSP is a measure of the ambient air pollutants with particles routinely monitored in this city (and elsewhere in Russia), the current (mainly Western) epidemiologic studies we used for dose–response assessment had focused mostly on the effects of PM_{10} or $PM_{2.5}$ (particulate matter < 2.5 μm in aerodynamic diameter). To proceed with the risk assessment, monitored levels of TSP (appropriately adjusted for temperature and humidity) were multiplied by 0.55 [a coefficient derived from parallel measurement data by Wilson and Spengler (12)]. to produce an estimate of the corresponding concentration of PM_{10}.

SO₂

We selected excess non-accidental mortality as the critical effect for SO_2 as well as for TSP for many of the same reasons. Although the literature base for deriving a risk function

is not as extensive for SO_2 as it is for PM, adequate information was available. Recent unpublished analyses of data from Krakow and Warsaw, Poland suggest that the coefficients relating SO_2 measurements to mortality (excluding accidents and homicides) range from 0.4 to 0.6% excess daily mortality per 10 μg/m³ increment in SO_2 concentration (13). To be conservative, we used the higher value of 0.6% to calculate the increase in mortality for Verkhnyaya Pyshma. Although results were not available at the time of the case study, a time–series analysis was performed by Katsnelson et al. (14) for the neighboring city of Yekaterinburg. This analysis yielded an estimated coefficient of 0.51% [95% confidence interval (CI), 0.28–0.74] per 10 μg/m³ for the SO_2 relationship to mortality (14), a result that is consistent with the relationship observed in the Polish data (13). All of the described coefficients are for acute SO_2 exposure, but they were used to approximate a response to chronic exposure based on the assumption that exposure occurs daily over long periods.

We used the estimated percent increase in mortality with the local mortality rate to estimate the excess mortality associated with TSP or SO_2 exposure.

NO₂

NO_2 is an irritant that is associated with increased respiratory symptoms, especially among asthmatic children. We used the risk relationship from an epidemiologic study reviewed by Hasselblad et al. (15). In this study, respiratory symptom occurrence was evaluated in 6- to 11-year-old children with gas stoves in their homes who had known average levels of NO_2. Hasselblad et al. (15) used data from this study to generate an equation for estimating the number of children affected by respiratory symptoms (Resp) as a function of NO_2 concentration (in milligrams per cubic meter):

$$\text{Log odds Resp} = -0.536 + 0.0275\,NO_2 - 0.0295.$$

We then applied the equation to exposure information for Areas I and II of Verkhnyaya Pyshma to generate an estimate of the total number of respiratory symptom cases occurring in the city annually.

Table 4. Main results of risk characterization.

Pollutants	Media (where detected)	Adverse effect	Predicted cases	Chief medium of exposure
Total suspended particles	Air	Acute mortality	46 Annually	Air
Sulfur dioxide	Air	Acute mortality	11 Annually	Air
Nitrogen dioxide	Air, water	Respiratory symptoms	19,000 Annually	Air
Lead	Air, water, food, soil	PbB above the "level of concern"	1,700[a]	Food, soil
Cadmium	Air, water, food	Nephropathy Nephropathy-induced mortality	10,600[b] 78 Annually	Food[c]

[a]Another assessment of children's psychological deficiency is expressed as the total IQ point loss compared with the IQ of American children not exposed to lead; for the whole population of children in this town this loss is ~5,450 points.
[b]During the lifetime of this population. [c]The contribution of soil was not assessed.

Table 5. Incidence of diseases of the urogenital system (*International Classification of Diseases, Revision 9,* codes 580–599) per 1,000 children in Verkhnyaya Pyshma, Sverdlovsk Region, and Russian Federation.

Year	Verkhnyaya Pyshma	Sverdlovsk Region	Russian Federation
1996	60.0	38.3	15.4
1997	65.4	39.6	16.3

Thus, the final risk estimate for NO_2 in this study was based on a risk function derived from a study of children but applied to the entire population and, as such, it contains the additional uncertainties contingent on extrapolation from one age group to another. However, it is likely to underestimate the health impacts for unidentified subgroups who are more susceptible to respiratory toxicity than healthy, school-age children, such as children with asthma or those who were too sick to attend school, or other more susceptible population groups such as infants, the elderly, or the chronically ill.

Lead

There have been many large studies of human populations exposed to lead, many of which have been reviewed by the International Programme on Chemical Safety (16). These studies often relate to specific age groups, such as the studies of developmental delays among children exposed to lead *in utero*, the relationship of biological levels of lead to IQ deficits or other psychological deficiencies in children, or the occurrence of hypertension and coronary heart disease in adults. We assessed two adverse health effects of environmental lead exposure in Verkhnyaya Pyshma: IQ deficits in children, an end point many scientists believe is a sentinel effect observed at lower blood lead concentrations than those causing any other adverse health effect (16); and premature mortality associated with lead-related hypertension among adults. In this paper we will report results of the risk assessment for children only.

Because the risk function relating IQ decrements to lead exposure was developed for blood lead levels (PbB) rather than for air concentrations of lead, an important first step was to estimate PbB levels in children in Verkhnyaya Pyshma. Because actual PbB data were not available for this town, we used three alternate approaches to estimate PbB levels. The estimates proved to be reasonably similar.

Estimation using kinetic modeling. We used the U.S. EPA Uptake/Biokinetic Model for Lead–Version 0.99d (U.S. EPA, Washington, DC) together with local lead concentrations in soil, water, air, and food to estimate likely blood lead values among Verkhnyaya Pyshma children. The outputs for this modeling procedure included both the average PbB levels of children in different age groups and the percentage of children with PbB levels > 10 µg/dL [the U.S. Centers for Disease Control and Prevention (CDC) "level of concern"]. The model has been positively validated for use in a Russian setting in three other industrial cities of the same region: Krasnouralsk, Pervouralsk, and Kirovgrad, where predicted levels were

compared to monitored PbB levels in four different groups comprising 831 children (17,18). In Verkhnyaya Pyshma, PbB levels estimated using this approach were as follows: the mean PbB level for children 3–7 years of age was 8.1 µg/dL for Area I and 7.9 µg/dL for Area 2 (8.05 µg/dL for the city as a whole), whereas 30% and 28.5% of children in Areas 1 and 2, respectively, had PbB > 10 µg/dL.

Estimation using hair lead levels. A second estimation procedure used a relationship determined by Bergomi et al. (19) in which observed hair lead levels (milligrams per gram) are multiplied by a factor of 1.6 to estimate PbB (micrograms per deciliter). In a recent hair lead study in 3- to 6-year-old children in Verkhnyaya Pyshma, Fomin et al. (20) found a mean level of lead in hair of 4.57 mg/g. The mean PbB level projected for Verkhnyaya Pyshma children using this approach was 7.3 µg/dL. The data did not permit separate estimation for Areas I and II.

Estimation based on comparative data from two Russian cities. The third estimation procedure capitalized on a blood lead study performed by Rubin et al. (21) among children from nearby Yekaterinburg (the regional capital) with the help of personnel from the CDC. The arithmetic mean PbB among 659 study children 2–7 years of age was 6.9 µg/dL, and the average air lead level was 0.15 mg/m³. If we assume that exposure to lead through food and water is not different between the two cities (a reasonable assumption in this case), we can use the observed differences in lead in air for the two cities, together with the observed levels of blood lead among children from Yekaterinburg, to estimate the average PbB level for children in Verkhnyaya Pyshma. The U.S. EPA has provided specific values for estimating the contribution of air lead to blood lead among children, including indirect pathways such as hand to mouth activities (22). The median of these values indicated an increase of approximately 4 µg/dL blood lead per microgram per cubic meter of lead in air. When this function was multiplied by the excess air lead concentrations in Verkhnyaya Pyshma (above those observed in Yekaterinburg), the predicted average PbB among children in Areas I and II were 6.49 and 6.34 µg/dL, respectively, and the city-wide average was 6.42 µg/dL.

Thus, estimates of the city-wide averages derived using the three techniques described above ranged from 6.42 to 8.05 µg/dL. The estimated PbB level derived from hair lead levels (7.3 µg/dL) was almost exactly in the middle of the range; therefore, we used this value to assess the average lead-induced IQ point loss risk among preschool-aged children.

We derived the risk function describing the exposure–response relationship for lead

and IQ point loss among children from a meta-analysis of seven studies (23). This function indicates that for a change in PbB from 10 to 20 µg/dL (expressed as the arithmetic mean) there is a decrease of 2.57 IQ points. We assumed that the relationship was linear in this range; thus a 1 µg/dL increase in PbB level would result in a decrease of 0.257 IQ points. For the population of children in Verkhnyaya Pyshma, the estimated IQ point loss was 5.450 points as compared to 1- to 5-year-old U.S. children during the years 1988–1991, using the U.S. National Health and Nutrition Examination Survey, Phase III (NHANES III) average PbB of 3.6 µg/dL as a baseline (24).

We assumed that the estimated aggregate IQ point loss among all children in Verkhnyaya Pyshma is likely be found among those with high PbB levels, that is, among the approximately 30% of preschool children whose estimated blood lead levels are > 10 µg/dL (based on the biokinetic modeling procedure described above). Taking into account that the preschool children population of this city is approximately 5,700, even such an assumption means that the average individual IQ point loss is only about 3 points per affected child. This loss is not considerable, although in a proportion of children with the highest PbB levels it would be much larger. We believe, however, that the estimate of the total IQ point loss per age group is of interest primarily for the risk assessment on the population level rather than on the individual level.

Cadmium

There are a number of non-cancer adverse health effects associated with exposure to cadmium; toxicity to the kidney tubules is the sentinel effect that occurs at the lowest doses (25–31). For the Verkhnyaya Pyshma risk assessment, we assessed cadmium-induced kidney disease using an elevation in B2u, a low-molecular-weight protein in urine, as an indicator of kidney damage. B2u is released at elevated levels in urine when kidney tubules have been damaged, allowing small proteins to be released rather than retained by the body.

Cadmium is a systemic toxicant once it enters the body by any route of exposure. Because it was found in air, food, and water in Verkhnyaya Pyshma, we felt that it was important to evaluate risk associated with both inhalation and oral routes of exposure. The approach used to estimate the risk of nephropathy and nephropathy-induced mortality was developed specifically for the Verkhnyaya Pyshma risk assessment. Briefly, the approach uses risk relationships derived by us from epidemiologic studies of a Japanese population living in the Kakehashi River Basin, downstream from a mine discharging

cadmium compounds into the river, together with what is currently known about cadmium nephrotoxicity (*29,30*). Nogawa et al. (*29*) focused on the B2u level of 1,000 µg/L as a marker of kidney toxicity, but in another study Nakagawa et al. (*30*) demonstrated that B2u > 300 µg/L was a marker of elevated mortality risk. Based on this information and the current levels used in clinical medicine to assess kidney toxicity, we used 300 µg/L B2u as an indicator of nephrotoxicity as well.

A series of steps in the estimation procedure led to the derivation of the following risk function: 55.9% of individuals may develop kidney disease as measured by a B2u level of 300 µg/L in a population exposed to 0.001 mg/kg/day. By applying this slope to exposure levels observed in Verkhnyaya Pyshma, we estimated that approximately 20% of the population might develop kidney disease (as defined by elevated B2u > 300 µg/L) in their lifetime. We multiplied the percentage at risk by the population of the city and determined that an estimated 10,597 people are at risk for kidney disease.

We estimated the relationship between cadmium exposure and death using a risk factor calculated from a study by Nakagawa et al. (*30*), which evaluated mortality associated with cadmium-linked B2u levels from 300 to 1,000 µg/g creatinine (the B2u/L may be assumed as an equivalent of concentration of B2u adjusted to the creatinine excretion). We determined a relative risk of 1.58. We multiplied the relative risk by the population with elevated B2u and by the city's background mortality rate to yield the estimated mortality.

Risk Characterization

A synopsis of the major results characterizing non-cancer risks due to TSP, SO$_2$, NO$_2$, lead, and cadmium is shown in Table 4.

We found that TSP, SO$_2$, and NO$_2$ in air pose significant risks for the population health in Verkhnyaya Pyshma. Based on the risk functions defined above, the fine particle fraction of TSP was estimated to cause almost 50 additional non-accidental deaths per year, whereas for SO$_2$ alone, about 10 such premature deaths per year occur in Verkhnyaya Pyshma. When we applied the respective risk function to levels of NO$_2$ observed in Areas I and II of the city, we estimated the annual number of cases of respiratory symptoms related to NO$_2$ exposure to be approximately 19,000 (note that one person can experience more than one symptom event per year).

Lead exposure was also determined to pose important risks in Verkhnyaya Pyshma. We estimated that the IQ score for the total population of 5,730 children might be from 4,146 to 6,551 points less as compared with that for a corresponding population of children in the

United States (according to NHANES III), this difference having been assessed based on comparing respective mean PbB levels. The total IQ point loss lies within a usual range of risk assessment uncertainties. The biokinetic model approach also provided an estimate of the proportion of the city's children that would be likely to have PbB levels > 10 µg/dL. This is the "level of concern" established by the CDC, or the level over which there is a possibility of adverse psychological effects. The model predicted that approximately 30% of the preschool children in Verkhnyaya Pyshma (1,676) would have levels > 10 µg/dL.

Cadmium was also found to pose substantial non-cancer risk to community residents. The most important medium of exposure for cadmium in Verkhnyaya Pyshma was food. We estimated that 10,600 persons would develop nephropathy during their lifetimes and that 78 deaths annually would occur from nephropathy in Verkhnyaya Pyshma. Although deaths from cadmium-induced kidney toxicity are likely to occur primarily among the elderly, children are also subjected to this toxicity; thus, deaths can occur at younger ages as well.

Moreover, it is feasible that children are not only more exposed (as to other environmental pollutants) but they are also more sensitive to the nephrotoxicity of cadmium. Children's exposure is associated with higher risk (per unit of cadmium dose), especially if we take into account a comparatively high (and steadily increasing during the last decade) incidence of kidney diseases among the children of the Sverdlovsk Region, and especially in Verkhnyaya Pyshma. Indeed, during the 2 years preceding the study, children in Verkhnyaya Pyshma had an incidence of urogenital disease that was approximately 1.5 times that reported for the region and approximately 4 times that reported for the whole Russian Federation (Table 5). A special epidemiologic study would be needed to test the hypothesis that this unusually high urogenital morbidity among local children is associated with cadmium exposure. However, whatever the real cause of this increased morbidity, there is no serious doubt that urogenital morbidity can, in some way, result in an enhanced sensitivity of children to the nephrotoxicity of cadmium.

We presented the results of this risk assessment to the decision makers in Verkhnyaya Pyshma so they could better understand both the nature and the relative magnitude of the risks associated with environmental pollution in their city and so they could better understand who would be affected in each case. Risks to children's health and development are important and deserve highest priority; for adults, there

should be priority control of exposures that can result in premature mortality (i.e., cadmium, TSP, and SO$_2$).

Conclusion

This study was one of the first risk assessment case studies performed in Russia, and it is certainly the very first study that deals with the assessment of multimedia–multipollutant exposure based on routine environmental pollution monitoring data. We drew many of the risk functions used for this analysis from the international epidemiologic literature. As is characteristic of risk assessment methodology in general (*10*), there are many uncertainties in the process, perhaps more than would be found in risk assessments conducted in countries where this methodology is well established; thus, many validated "normal" or "average" population values are available for use (e.g., normal PbB levels for different age groups). Although specific local information was often missing, it is possible to benefit from international studies and to substitute validated norms from other countries where necessary in order to produce the needed estimates of population risk.

Decision makers usually prefer the quantitative estimates of health effects that can be produced by using a risk function approach to a more qualitative indicator of risk. As the use of health impact assessment becomes more widespread internationally, the gaps in local or regional information (such as population distributions of blood lead, IQ point scores, and blood pressure), which may exist in countries where risk assessment is just beginning to be practiced, should be addressed so that environmental health decisions can be made on increasingly accurate estimates of the negative health consequences of environmental pollution.

Based on the results of this risk assessment case study, the administration of the municipality Verkhnyaya Pyshma approved an action plan aimed at managing priority risks, especially among children, and at improving environmental pollution monitoring.

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