Of Jugglers, Mechanics, Communities, and the Thyroid Gland: How Do We Achieve Good Quality Data to Improve Public Health?

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Our knowledge about the distribution of exposures to toxic chemicals in various communities is limited. Only about 6% of approximately 1,400 toxic chemicals have been identified in surveys. Even for those chemicals that are measured, information is often insufficient to identify smaller populations at high risk. The question is whether information about the distribution of diseases in communities can help identify environmental risks, indicate areas of concern, and thus substitute exposure information. Thyroid disorders represent a large group of diseases that cannot be recorded into registries because of the lack of clear caseness; community-based monitoring of subtle health effects is needed. Thus, to identify potential health risks in communities, epidemiologic studies including effect and human exposure monitoring are necessary. However, to overcome the limitation of non-systematic case studies, the development of a network of exposed communities concerned about exposures is proposed. A network would provide assessments of exposures and health outcomes, with different communities mutually serving as exposed and control groups. Such a network would foster communication and prevention measures within communities often left out of the dissemination of information about risks identified in studies conducted with residents of these communities. Key words: community, design, environment, participation, PCBs, risk communication, thyroid, thyroxine, triiodothyronine, TSH. — *Environ Health Perspect* 109(suppl 6):863–869 (2001).

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Processes and interactions in the detection, evaluation, and management of environmental threats in communities or public health can be described from different points of view. A recent report of the Pew Environmental Health Commission emphasized the “need of a modernized public health defense system that will protect our citizens and their communities from chronic health conditions and environmental risk” (1). The report focused on administrative and monetary aspects and suggested more resources for the public health practice but did not deal with issues involving how science and communities interact. A recent description of modern challenges of environmental epidemiology emphasizes the need for a population and ecosystem level. However, the suggested approach did not address the interaction of researchers and communities (2). Within the field of environmental research, epidemiologists are at the forefront of community interaction. When examining people during data collection, environmental epidemiologists learn about their concerns. Nevertheless, the history of misunderstanding and mistreatment of communities is long (3). This article presents a weak-point analysis of environmental health research for outcomes not routinely registered, focusing on thyroid disorders as one example. The work attempts to explain why environmental research is done, with, and in communities requires a more complex scientific approach. The weak-point analysis, ranging from molecular explanations to communication approaches, is structured in six parts:

- In an ideal world
- Thyroid disorder: historic and modern challenges
- Detection of environmental problems and community experience with experimental hypothesis testers
- The juggler and the mechanics
- Beyond mechanistic research: requirements for environmental research that serves public health
- Models for community-oriented environmental approaches

In an Ideal World

In an ideal world, epidemiology serves public health through a problem-solving cycle. Whenever the community, physicians, or scientists identify a health-related issue, epidemiology initiates the definition and quantification of the problem. After priorities have been set and measures conducted to diminish public health problems, epidemiologic work focuses on quantifying potential results. Finally, new assessments serve as input for an adapted new round of the problem-solving cycle.

In an ideal world, all exposures are monitored everywhere and all people are informed in order to make an educated decision whether to accept or attempt to reduce exposures. We are, however, far away from the ideal world. The U.S. General Accounting Office concluded that surveys of the Department of Health and Human Services and the U.S. Environmental Protection Agency have measured about 6% of approximately 1,400 toxic chemicals. Even for those chemicals that are measured, information is often insufficient to identify smaller populations at high risk (4).

We use health outcomes to identify exposure, partly because of our distance from a world with ideal exposure information and for practical reasons, but primarily because for rare or unexpected health risks, only an increased frequency of diseases indicates the area of concern. In fact, in the last three decades the identification of toxic hazards in communities and workplaces often stemmed from lay observations, not from exposure monitoring or human biomonitoring (3). Identification of the hazards by lay observations requires, however, that individuals notify the association of health effects and pollutants, community residents share information, and community groups organize to pursue investigations. The limitations of this process are obvious. Communities at the lower end of the socioeconomic scale are disadvantaged, which can produce environmental injustice. Modern sociology describes the capacities of communities to master their environment as social capital (5,6). Given that we might have to employ disease to identify environmental health risk, there are two alternatives: monitor all diseases and/or empower communities.

Ideally, all diseases would be monitored everywhere. All people would be informed and subsequently do their best to reduce the burden of diseases and the related critical exposures. An attempt to follow this ideal is presented by the small area health statistics in the United Kingdom (7–9) or the proposal of a nationwide health tracking network in the United States (1). This common-sense approach requires that exposure causes manifest diseases, which in turn could be monitored. This limits health statistics to outcomes such as mortality, cancer, and malformation.
This approach may be capable of detecting disease with a short latency period such as birth defects (latency period: about 9 months) around chemical waste sites (10–12). However, this approach is inappropriate for many subclinical effects such as minor reductions of intelligence, alterations of human reproduction, and subtle effects on the thyroid. A second requirement is that manifestation of the disease occurs shortly after exposure. When relying on small area health statistics and related exposures, diseases with long latency periods can hardly be attributed to past exposures.

Questions posed by exposed communities or public health are far more complex. Regarding thyroid disorders, there are at least four questions from potentially exposed and educated communities:

- Are we exposed to chemicals that affect the thyroid as well as thyroid hormones?
- Will we develop manifest thyroid disorders after experiencing endocrine disruptions?
- Will our children develop thyroid disorders because of exposure in early life?
- Will our children develop mental delays if exposed to endocrine disruption in utero or in childhood?

### Thyroid Disorder: Historic and Modern Challenges

These questions may be exemplified with a historic example (simple exposure and etiology) and with one actual example that challenges the simple assessment of health risks (complex etiology).

#### The Historic Example

One disorder of the thyroid gland, thyroid enlargements (goiters), was recognized around 3000 BC. For centuries, endemic goiter had been recognized in mountainous districts. As early as the beginning of the 19th century, goiters were attributed to insufficient iodine in the diet. Additionally, lack of iodine in pigs was recognized as a cause of endemic cretinism. A major outcome of maternal goiter was mental retardation (13). Thirty percent of young men were afflicted with a large goiter and were thus unfit for military service. Deaf mutism (the inability to speak due to congenital or early affliction of profound deafness) was associated with the prevalence of goiter and in the survey served as a marker for cretinism, which was variable in its manifestations and therefore hard to define.

It took centuries to identify the environmental cause. In the 19th century, even though the lack of iodine had not yet been identified, sea algal extracts, rich in iodine, were used to treat the disease (14). Iodination of salt was then introduced in 1922 in Switzerland. No new endemic goiter born after 1930 have been identified. Goiter disappeared rapidly in newborns and schoolchildren, more slowly in army recruits, and incompletely in elderly adults (13). Historically, for goiter, the health problem-solving cycle was completed. It is clearly a public health success story. Thyroid diseases and cretins could be prevented, although not all mechanisms were investigated and tested. This example, however, describes a simple relation, which might explain its success. First, for the regions involved, iodine deficiency was the single major cause. Second, no community involvement was required to understand routes of exposure, the development of the disease, or the implementation of preventive measures (iodination).

#### The Modern Example: Complex Effects of Polychlorinated Biphenyls on the Thyroid

The potential impact of halogenated organic compounds (HOCs) such as dioxins/furans and biphenyls on the thyroid gland was first identified in wild animals (15,16). The effects seem less dramatic but more complex in comparison with those caused by the lack of iodine. Nevertheless, as with insufficient iodine, there may be definite direct and indirect effects on the fetus, mediated by maternal exposures.

Every cell in the body depends on the thyroid hormones thyroxine (T4) and triiodothyronine (T3) for regulation of metabolism. The normal thyroid gland produces about 80% T4 and about 20% T3. The latter possesses about 4 times the hormone potency of T4. The thyroid gland is under the control of the pituitary gland. When the level of thyroid hormones (T3, T4) drops too low, the pituitary gland produces thyroid-stimulating hormone (TSH), which stimulates the thyroid gland to produce more hormones (feedback). Under the influence of TSH, the thyroid gland manufactures and secretes T3 and T4, thereby raising their blood levels. Thyroid hormones (T3, T4) are transported in the blood by proteins, T4-binding globulin (TBG), also called transthyretin or T4-binding prealbumin. Unbound T3 and T4 (free T3, T4) are metabolically active. Thus, an alteration of thyroid hormones can result from a change in concentration of the transport proteins and from competitive binding of xenobiotics to these proteins.

For the fetus and in childhood, thyroid hormones are essential for the development of brain function and the growth of cells. Deficiency of thyroid hormones can subse-
the thyroid. Hypothyroidism results when autoantibodies bind to the proteins thyroglobulin (Tg) and thyroid peroxidase (TPO), thereby blocking the uptake of iodine required for the normal production of thyroid hormones. There is evidence that HOCs are associated with thyroid antibodies (Table 1). Tg antibodies were detected in 8 (19.5%) of 41 Yusho patients with PCB concentrations higher than 3.0 ppb and in only 1 (2.5%) of 40 patients with PCB concentrations lower than 2.9 ppb (3.2). Residents living in a contaminated development area had an increased prevalence of antibodies against human TPO (TPO titer >70 U/L) compared with residents of two areas with less or no pollution (19.1% compared with 10 and 12.6%) (3.3). In the Slovakian study of 190 female workers in a factory that previously produced PCBs, a significantly increased prevalence of TPO (28%) was detected compared with 20% in 482 controls (30). There was also a higher prevalence of Tg antibodies in women (21%) and antibodies against the TSH receptor in men and women (10%).

Potential overproduction of T3 and T4 as a reaction to autoantibodies, however, is just the opposite of what is predicted as a result of the endocrine reaction to PCBs. Some of the studies included in Table 1 identified a higher prevalence of antibodies against TPO and Tg and no increase of TSH (30) or no PCB effect on thyroid hormones (3.2). It is possible that these negative findings result from mixing endocrinologic and autoimmune effects (PCBs → T4↑ and thus TSH↑ versus PCBs → autoantibodies → T4↑). Thus, studies that identify specific effects are required to provide an unconfounded assessment of the HOC-thyroid association.

Research results are inconclusive. However, adverse effects cannot be excluded, as the studies did not distinguish endocrine and immune effects and different time windows of exposure (childhood vs adulthood). One reason for the insufficient state is that studies were not broad enough and did not include all markers needed to evaluate potential associations between HOC in the environment and effects on the thyroid gland. Another reason is that most studies were not committed to serve public health but to test some hypotheses. Community participation, for example, in the study with the PBB exposure (Table 1), would have caused researchers to contribute greater efforts toward understanding the PBB-hypothyroidism association, as communities and exposed individuals need the most complete information to manage the disease and to prevent long-term effects. For instance, in the study with residents who lived on the waste site (Table 3), it was the residents and exposed individuals that claimed to have increased levels of thyroid antibodies.

Thus, to make the thyroid–HOC associations more complex, we have to add another
question to the four questions raised by communities (see above): Are contradictory results (Table 1) due to a different involvement of autoimmune and endocrine pathogeneses?

These five questions are highly interdependent, similar to five balls juggled in the air at the same time. The state of the art and also educated communities thus pose complex questions and deserve the best quality answers. However, the monitoring systems focused on manifest disorders that can be registered, such as birth defects and cancer, will not be able to answer these questions. Thyroid disorders are thus an example of a large group of diseases that includes, for example, infertility, minor reduction of intelligence, asthma, and allergic manifestation. They may be caused by environmental contaminants and detected by concerned communities, but they cannot be detected through existing disease registries, as these diseases do not regularly develop into definite cases. Nevertheless, these disorders affect the public health.

If monitoring of registered diseases does not work, what are alternative avenues to detect diseases, conduct investigations, and inform the public about potential environmental risks? The next three sections are devoted to this question. First, we describe experiences of communities with experimental hypothesis research; second, the experiences of environmental epidemiologists with experimentally oriented funding is reported; and third, alternative strategies are outlined.

Detection of Environmental Problems and Community Experience with Experimental Hypothesis Testers

New kinds of exposures, sometimes detected by chance, attract research. One example is the PBB exposure in Michigan. St. Louis, Michigan, is a low-income community that was the site of Michigan Chemical (A.K.A. Velsicol) from 1935 to its closing in 1978. The production included inorganic products (magnesium oxide), rare earths, and a variety of halogenated organic products such as 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethyl-ene (DDE) without accounting for the possibility of others (PCBs and PBBs). Findings may show a significant association of a particular health outcome with DDE, but in reality the risk was not truly associated with DDE but with PBBs or PCBs. Such spurious associations can be minimized by carefully designed studies that need to be sufficiently broad to avoid overly narrow exposure assessments. In addition, regarding the assessment of health outcomes in a public health setting, epidemiologic research cannot provide the best quality information if it is limited to focusing on a single risk factor [for instance, 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDE)] without accounting for the possibility of others (PCBs and PBBs). Findings may show a significant association of a particular health outcome with DDE, but in reality the risk was not truly associated with DDE but with PBBs or PCBs. Such spurious associations can be minimized by carefully designed studies that need to be sufficiently broad to avoid overly narrow exposure assessments. In addition, regarding the assessment of health outcomes in a public health setting, epidemiologic research cannot provide the best information if restricted to only one health outcome. It should be the aim for any research project to provide beneficence to individual subjects, communities, and society as a whole. This ethical responsibility entails providing the maximal possible benefit, which requires using a broader and more comprehensive approach.

The second dilemma is that mechanistic hypothesis-testing research often does not fit the needs of individual communities and public health. Hypothesis-testing research is often focused on specific scientific questions. Its objective is publication of findings, a necessity for the researcher. However, there are no incentives for scientists to engage in risk communication or community participation. Communities have broader questions regarding their health.

Environmental epidemiology is at the forefront of new research strategies. An environmental epidemiologist has to consider a complex scientific setting as well as collaboration with communities. Considering these requirements, an environmental epidemiologist is like a juggler who knows how to juggle four balls effectively. At the request of the community, however, the juggler has to add a ball and keep five balls in the air at the same time. Thus, the epidemiologist needs funding to prove that he can juggle five balls.

The Juggler and the Mechanics

To obtain funding, a juggler who can keep four balls in the air at the same time approaches a review board of three mechanics for funding to prove he can juggle five balls. He wants to study the special techniques required to keep the balls in the air. He suggests scientific models and methods to approach this complex field as well as ways of communication with the citizens. The first mechanic suggests that the juggler focus his research; he should study the mechanics of one ball at a time. The second mechanic agrees and explains that in his laboratory five related experiments could not be run simultaneously and that there is no way to evaluate the meta-mechanics of five balls in the air. In addition, the third mechanic decides that the juggler’s approach is much too ambitious. The third mechanic suggests that the juggler not communicate with the communities before his results are confirmed by other studies. Funding is denied. The juggler is advised to focus on a specific hypothesis in experimental research, focus on science, and stay away from community involvement.
Beyond Mechanistic Research: Requirements for Environmental Research That Serves Public Health

There is no doubt that experimental designs have their strengths. However, when applying a series of oversimplified designs to a complex problem, the disadvantages will outweigh the advantages such that public health concerns cannot be addressed properly. Hypothesis-testing designs attempt to mimic experimental approaches, even in public health settings. Hypothesis-testing research often focuses on one outcome, preferably a single exposure, and has one main goal, namely, scientific publications. Community-based research has to consider real-life situations with multiple focuses (outcomes) and multiple exposures. The guiding objectives are risk communication and the development of strategies for problem solving (Table 5). As stressed in environmental epidemiology textbooks, public health research requires a long-term involvement and a compromise between scientific objectives and community participation that will alter the rigid scientific model. This approach has not yet been accepted by some funding agencies that ask for nonflexible mechanistic approaches.

However, there are alternative and more efficient models in public health science than mechanistic hypothesis testing. Modern epidemiology can incorporate complex scenarios, increase generalizability, and address public health concerns when not restricted to mechanistic hypothesis testing. There should be funding and equal opportunity for both types of research.

Models for Community-Oriented Environmental Approaches

To overcome these limitations, research and state agencies, communities, concerned citizens, and nongovernmental organizations need to integrate their environmental health research efforts. Because our knowledge is limited about the distribution of exposures to chemicals in communities and their association to health, we have to integrate human biomonitoring and health monitoring. Instead of conducting the three aspects of environmental health research separately, namely, human exposure monitoring (biomonitoring), research into the association of exposures and health effects, and risk communication with community, we should use our resources more carefully, with better planning, and foster the collaboration of different research groups, such as those in clinical trials, for the common good of public health.

One suggestion is the formation of a network of communities concerned about exposures. In addition to the common representative national sampling, the network could provide assessments of exposures and health outcomes, with different communities mutually serving as exposed and control groups. As research would directly address community concerns, such a network would foster community participation and convey risk communications (Table 5) (42). Communities benefit as they gain information on regional health risks. Research benefits when a set of multiple communities with different exposures, participating in such a network, provides access to study groups, collects a complex range of exposures, and allows the contrasting of a variety of health effects with different exposures and varying exposure levels. For example, of 10 participating communities, mercury may be elevated in 3; however, we determine the background levels from the other 7 and can thus investigate the extent of the mercury problem. We may have a complex exposure of mercury and PCBs in 2 communities and can investigate whether markers of effects are associated with mercury, PCBs, or both.

To show that rudimentary networks exist and that compromises between concerned communities and research can be guided, some examples are listed below.

| Isolated hypothesis-testing research world | Community-participating research world |
|------------------------------------------|----------------------------------------|
| Test if E–D association is true regardless of the specific community life styles. | Focus on occurrence of exposures and diseases in community life. |
| Test the E–D association. | Understand the E–D association. |
| Assume that it is sufficient to know initial exposure data to explain subsequent diseases. | Understand why individuals are exposed within the community and the routes of exposure. |
| Collect information about paths of exposure (E1 → E2). | Collect information about paths of exposure (E1 → E2). |
| Observe a population over a long or short period, with short phases of individual involvement, typically during data collection. | Observe a population over a long period with repeated measurements. Enlist community involvement and participation. |
| Analyze the data on the E–D association. | Analyze the E1 → E2 → D1 → D2 → D3 associations. Understand the underlying molecular and biologic processes and the different options to reduce the risk of early and final stages in the pathogenesis. Communicate findings and prevention strategies to the community. |
| Publish the results about the E–D association. | Publish the results within the scientific world and for the community. |
| Assume that knowledge on the E–D association is sufficient to change public health. | The mechanism of E–D need not be entirely clear to prevent adverse disease outcomes. Participation of community groups is required to develop prevention strategies. |

Abbreviations: D, disease; E, exposure.
Small-Scale Collaboration with Community Participation

Communities in Hesse, Germany, requested and participated in a study on a toxic waste incinerator. The study also included communities that were not exposed to the toxic waste incinerator and gathered a great variety of exposure and health data in children (51–56). The data included questionnaire information, biomonitoring of metals and organochlorine compounds, laboratory data on thyroid hormones, humoral and cellular immune responses, lung function data, determination of air pollution, etc. Most of the information was repeated in two or three follow-up surveys. This richness of information is unusual for some funding agencies and a threat to reviewers who prefer to focus on a single issue. However, a more complex approach with integration of molecular, social, and communication issues is not an impossible mission. Exposed and non-exposed communities profited from the depth of the investigations and learned about exposure risks to children in their resident areas (e.g., lead from water pipes). As investigations were harmonized with other studies, the project also contributed to the collection of national reference data (43). The study also achieved openness, a goal proposed in environmental epidemiology (57), as representatives of concerned citizens, the local health department, and physicians participating in the project requested additional and detailed information about methods and results. In effect, communities were able to control the project and trust its risk assessment. Scientifically, the richness of the data was a treasure for etiologic research.

Compromises between Communities and Science: The Leapfrog Procedure

Researchers have to compromise between scientific and community goals. In the last example (toxic waste incinerator), researchers and communities decided not to test all possible or plausible hypotheses between exposures and health markers, but rather to apply a leapfrog procedure. The procedure requires that both exposures and health markers are increased in the same communities before the association between the two dimensions is investigated based upon individual observations. This was the case for PCBs and thyroid hormones, for example. After having demonstrated that the level of PCBs was significantly higher for children of the toxic waste site area (51) and that the levels of thyroid hormones were lower in this area (52), the association of PCBs and thyroid hormones was investigated (53).

It is suggested that such networks, as well as other collaborative projects, need scientific steering groups. Second, such networks require local collaboration with the communities. Researchers have to provide information on their methods and findings. Citizens have the right to request alternative approaches. The collaboration may be arranged as round-table meetings of researchers, local health authorities, and concerned citizens. A third component is meetings of representatives of the communities. The communities should exchange their experiences in order to improve the collaboration and the impact of the research on public health.

Regarding the costs, there are hundreds of disconnected studies funded by different agencies on different environmental topics. The major costs in epidemiologic projects involve recruitment and participation in the study. If each study would add some research modules to its protocol, we would gain important information for different populations; first, on the distribution of a variety of exposures; and second, on the distribution of health outcomes that do not fit into administrative disease registration. Scientifically, we would gain a rich data set and could test a variety of exposure–health associations. The network of exposed communities, therefore, would require collaboration but ultimately would reduce costs.

Imagine that the juggler who approached the review board is not asked to focus on one experimental question that may provide a few mechanical explanations but is asked to carry out some additional work for the common good of public health. Protocols and funding would be provided for his research questions and for the additional work. He is, however, requested to participate in a network of research with exposed communities.

In summary, a network of communities can provide an epidemiologic laboratory. Research involving diseases with complex etiologies and pathogeneses requires not only intricate molecular methods but also increased community participation. There are three reasons for these needs: to conduct long-term community studies, to understand the environmental condition, and to lay groundwork for prevention. Community-based research can integrate processes that occur on a molecular, individual, and community level. Information on real life is necessary to gain a better understanding of exposures (use of pesticides, traffic, etc.) and how to prevent diseases. Basically, the network can integrate exposure assessment, human biomonitoring, and effect monitoring on a local/community level.

Thus, to advance our understanding, we must bridge hypothesis-oriented research and community-oriented approaches (Table 4). The Ottawa Charter for Health Promotion has stated this succinctly:

Health promotion works through concrete and effective community action in setting priorities, making decisions, planning strategies and implementing them to achieve better health. At the heart of this process is the empowerment of communities—their ownership and control of their own endeavors and destinies. Community development draws on existing human and material resources in the community to enhance self-help and social support, and to develop flexible systems for strengthening public participation in the direction of health matters. This requires full and continuous access to information, learning opportunities for health, as well as funding support. (58)

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