Collaboration between the World Health Organization and the National Institute of Environmental Health Sciences:

Highlights from 30 years of Partnership

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Foreword

Dear Colleagues,

It is with great pleasure that we present to you the highlights of nearly 30 years of collaboration between the National Institute of Environmental Health Sciences and the World Health Organization to promote global environmental health. During this period, the world has witnessed a dramatic transformation, not only in the understanding of the links between environmental chemicals and human health, but also in the knowledge of how to prevent diseases associated with the environment and how to partner with communities to ensure positive and lasting change. There has also been a transformation in the ways that scientific information is shared and communicated; in the 1980s most people had never heard of the internet and it was necessary to publish documents and send them around the world by mail in order to assure that the most up to date information was shared. It often took months from the time a new finding was published until it reached people who needed the information. Today, scientific information circles the globe and reaches scientists, policymakers, and community members on the same date it is released. This document is dedicated to the memories of three individuals who played critically important roles in ensuring the success of this collaborative agreement: Dr David Rall, Dr Thressa Damstra and Dr Jenny Pronczuk de Garbino. It was their hope that in the future the knowledge and information about global environmental health would help people to work towards healthier environments and healthier communities around the world.

Maria Neira
Director
Public Health and Environment
World Health Organization

Executive Summary

For nearly 30 years, the World Health Organization (WHO) and the National Institute of Environmental Health Sciences (NIEHS) have worked together under the auspices of a cooperative agreement to enhance global environmental health through research, training, capacity-building, and information-sharing activities. In advancing activities throughout this exceptional collaborative timeframe, both WHO and NIEHS utilized their respective strengths, capacities, and leadership roles in the interest of advancing global public and environmental health. The earliest years of the collaboration focused on a chemical-specific or target-organ approach, characterized by the production of single-issue Environmental Health Criteria documents. By the late 1990s the organizations moved towards addressing environmental health and chemical safety issues in a more integrated way, taking into account multiple and cumulative exposures and the resulting co-morbidity. The exceptional cooperative activities resulted in increased global attention and innovative research in several emerging topic areas, notably endocrine disrupting chemicals, toxicogenomics and biomarkers, integrated risk assessment methods, and the health of vulnerable populations including children.

History and background

This report does not represent an exhaustive record of all activities covered in the lengthy span of the WHO-NIEHS Cooperative Agreement. Rather, it aims to present in broad terms the rationale for creating the Cooperative Agreement, the approach taken to the work it supported, and how its key activities and outputs adapted to reflect major events and changes in the international policy environment throughout this period. In this way, the overall aims and achievements can be seen across the three decades, and the effects on the wider arena of global chemical safety.

Hundreds of thousands of chemicals circulate widely in the environment, affecting the health of rich and poor alike, in both developed and developing countries. In many ways, these chemicals contribute directly to economic development and productivity, by enhancing countries' capacity to boost their agricultural and industrial production. Many of these chemicals, however, pose severe health risks.

Types of hazard – key examples

- Chemical: Bhopal, India, 1984: 2,000 dead, 8,000 deaths from chronic effects, an estimated 50,000 totally or partially disabled
- Radiation: Chernobyl nuclear reactor explosion, Ukraine, 1986. Estimated 40,000 short-term deaths, half a million exposed to radiation long-term.
- Volcanic action – release of gases and chemical compounds: in 2010 alone, Mount Eyjafjallajøkull in Iceland caused global disruption to air travel for weeks. Mount Merapi's double eruption in Indonesia caused evacuation and loss of livelihood of tens of thousands of poor people.
- Transboundary waste dumping: usually from industrialized countries to developing nations, often in sub-Saharan Africa. A case in Cote d'Ivoire in 2006 resulted in several deaths and 44,000 seeking medical help. Financial implications were estimated at US$130 million.
- Oil spills: Deepwater Horizon 2010, Exxon Valdez 1989, Niger Delta (ongoing)
  In addition to environmental and wildlife damage, and loss of livelihood, the food chain is affected through oil-contaminated zooplankton which are an important source of food for many species of fish and whales.
- Milk contamination, 2008: 50,000 babies affected with kidney stones and renal failure, and 4 deaths, through addition of melamine to infant formula in China.

These may be felt immediately and directly, as in the accident at Bhopal, or in the numerous chemical spills and other industrial disasters that may not make headlines but do cause substantial health damage. Or they may, along with other environmental threats, become a "creeping catastrophe" that insidiously eats away at health security, leading to decreases in national productivity and increases in healthcare needs. For the very poor and vulnerable with few social and economic safety nets, environmental

chemicals can and do spell disability and early death. Examples abound, and those given below are only illustrative of a wide and growing problem.

Despite all precautions, legislation, regulation and international conventions existing in this domain, the continuity of major environmental disasters over decades underscores the need for a strong coordinated global response.

Genesis of the International Programme on Chemical Safety

Following discussions at the seminal 1972 UN Conference on the Human Environment in Stockholm, the World Health Assembly requested WHO to study the problem of long-term strategies to control and limit the impact of chemicals on human health and the environment. This followed increasing recognition that the ever-increasing trade in and use of chemicals could only increase the threats to environmental health both in the present and the future. Therefore, a collaborative approach to a sound and thorough evaluation of their impact was needed, which would have the benefit of avoiding duplication of effort while putting scarce resources to the best possible use.

In 1977, the World Health Assembly therefore requested the Director-General of WHO to examine, in collaboration with appropriate national institutions and international organizations, the possible options for international cooperation in this area. A Programme on Chemical Safety was then implemented, through the establishment of a central unit at WHO HQ in Geneva, to plan and coordinate the work carried out by a network of national and international institutions.

The International Programme on Chemical Safety (IPCS) was initially conceived as a WHO activity; however, the need to ensure close collaboration and coordination with various organizations in the United Nations system was underlined in Resolution EB63.R19 of the WHO Executive Board. To ensure appropriate input from the UN bodies most closely concerned, a Memorandum of Understanding was signed between WHO, ILO and UNEP in April 1980, making the IPCS a tripartite, collaborative initiative. Close collaboration was also established with the Food and Agriculture Organization of the United Nations (FAO). Agreements were later signed with a number of organizations working in related areas, including the Organization for Economic Cooperation and Development (OECD) and the European Union. On questions of chemical carcinogenicity, the

International Agency for Research on Cancer (IARC) in Lyon, France, was the Participating Institution taking the lead role.

That WHO should function as the headquarters and coordinator of the newly-created IPCS was a decision logically based on the organization's role and status as the world's leading public health agency, with global outreach particularly throughout the developing world. This new programme was charged with ensuring a science-based approach to furthering the challenges to health of environmental chemicals - challenges that could only increase with time (EHP 106:4, 1998). The US National Institute of Environmental Health Sciences (NIEHS) was the most prominent among the wide range of national and international stakeholders supporting this measure, providing not only technical but also financial support from the outset.

The main objectives of the IPCS can be stated as follows:

- to establish the scientific basis for assessing risk to human health and the environment from exposure to chemicals; and
- to provide technical assistance in strengthening national capacities for the sound management of chemicals.

These have remained the core operational principles.

Interregional Research Unit

A special role in the new programme was played by the NIEHS, a Participating Institution of IPCS. Under the leadership of Dr David Rall, Director of NIEHS at that time, an Interregional Research Unit was initiated and housed at NIEHS in Research Triangle Park, North Carolina, USA. The Interregional Research Unit comprised a small professional and support staff, actively supported by the technical staff of NIEHS. It planned and implemented projects and activities of particular interest to WHO and NIEHS, principally in the areas of mutagenicity, effects of chemicals on specific organ systems, and the toxicology of selected chemicals. The Unit cooperated with the WHO Regional Office for the Americas (AMRO/PAHO) to enhance implementation of IPCS activities in that region.

At the outset, a number of Regional Research Units were envisaged in various geographic areas, to be run along identical principles, so that a research network could operate globally. This expansion did not take place,

however, so the original Interregional Research Unit in North Carolina remains the only one.

Involvement of Member States

There was a steady growth in the number of Member States actively participating in the programme through their national institutions. Agreements with respect to collaboration between IPCS and governments or individual institutions were formalized in Memoranda of Understanding (MoU), signed by the most relevant Executive Head of Agency – normally the Director-General of WHO – on the one hand, and the representative of the most closely involved ministry or governmental institution on behalf of the government, on the other hand. This MoU was therefore the basic instrument by which those governments choosing to support the IPCS undertook a commitment to implement specific IPCS activities through their national institutions (Participating Institutions) and to provide resources, both to the WHO-based Central Unit and to their national institutions.

Advisory Bodies

IPCS had a Programme Advisory Committee (PAC) composed of 20 members appointed in their personal capacity. It represented those Member States actively supporting IPCS activities. It provided independent advice on the policy and priorities of the programme, and made recommendations regarding the selection of national IPCS participating institutions. Other intergovernmental and nongovernmental institutions with interest in the area also attended meetings of the PAC. The PAC was a separate entity from the Scientific Advisory Committee (SAC) established to guide and advise on that portion of IPCS's work funded through its Cooperative Agreement with NIEHS – the subject of this report.

IPCS operated along principles that characterized many UN programmes required to exercise global responsibilities with limited human and financial resourcing. Operating with limited core or seed funding from donors in relevant fields of operation, it was essential to harness the interest and assistance of expertise in all parts of the world to ensure the continuation of activities of mutual interest. As pointed out in an article for Environmental Health Perspectives written by Dr Thressa Damstra, Head of the Interregional Research Unit from 1997 to 2007, a small core staff called in relevant expertise based on need for each different activity,

be it the development of a normative guideline or carrying out a pilot research project (EHP Vol.106:4, 1998). In this way the most recent knowledge was shared and discussed globally, while duplication of effort was avoided.

The first WHO-NIEHS Cooperative Agreement was created in 1982, marking the start of a range of research, training, capacity-building, and information-sharing activities spanning a nearly thirty-year period. In advancing activities throughout this exceptional collaborative timeframe, both WHO and NIEHS utilized their respective strengths, capacities, and leadership roles in the interest of advancing global public and environmental health. Across this time span, a number of seminal international summits and conferences took place, from UNCED in 1992 to the globally-adopted framework of the Millenium Development Goals in 2000. Advances in knowledge, coupled with a changing policy landscape, radically altered how environmental health and chemical safety hazards were perceived and acted on. In turn, the activities undertaken by NIEHS and WHO reflected and adapted to these needs.

Change in focus

While the earliest years of the collaboration had focused on a chemical-specific or target-organ approach, characterized for example by the production of single-issue Environmental Health Criteria documents, by the late 1990s it was considered more appropriate to global concerns to address emerging environmental health and chemical safety issues in an integrated way, taking into account multiple and cumulative exposures, and the resulting co-morbidity. The wider canvas this created posed greater challenges, requiring more to be accomplished with limited resources.

There can be little doubt that the change in direction was also influenced by the global policy directives that emerged from the United Nations Conference on Environment and Development (UNCED) in 1992. Following twenty years after the Stockholm Conference of 1972 and consolidating the world's position on environment and sustainability, UNCED's implementation arm – Agenda 21 – contained a clear series of recommendations in its Chapter 19 to guide work on the sound management and regulation of chemical production and trade on the one hand, and the essential task on the other hand of ensuring that people everywhere had appropriate access to information on chemical handling and exposure.

To work on this scale with restricted resources, it was clear that a broad, innovative approach was needed; hence a framework of proactive partnerships was adopted. To keep this wider approach on track, the earlier *ad hoc* Scientific Advisory Committee (SAC) established to provide expert advice and guidance to work carried out under the WHO-NIEHS Cooperative Agreement was converted in 2000 into a standing committee, meeting every 12-18 months.

I. Norms, guidelines, and good practice tools

The early years of the WHO - NIEHS Cooperative Agreement period can be characterized by intensive production and publication of norms and guidelines, and good practice tools. In an effort to contain the actual and potential damage from thousands of known and unknown chemicals that were bombarding the environment in both developed and developing countries as technical and industrial capacity expanded, dozens of chemicals were prioritized and evaluated by teams of independent scientists. Information was primarily drawn from existing reliable reports, and compiled by teams of experts in that particular domain into documents focusing on a specific chemical or related hazard (Spheres, EHP Vol.106:4, 1998). Hundreds of publications were produced and disseminated throughout the Agreement period, drawing on the highest levels of expertise available globally.

Environmental Health Criteria series

Possibly the best-known of all the IPCS publications were the scientifically rigorous, internationally peer-reviewed Environmental Health Criteria series (EHC). This series, which comprises 239 volumes, has provided both developed and developing countries with an exhaustive and authoritative source of information on a wide range of key chemical issues and problems, drawn on by international and national bodies for purposes of teaching, research, and national legislation/policy-making. As recommendations on the prioritization of the chemicals to be thus evaluated were made by country representatives, rather than by IPCS, the value and subsequent use of the series at national level was assured from the outset. Of the 207 Environmental Health Criteria documents produced by 1998, eleven were prepared specifically under the aegis of the Interregional Research Unit

with the financial support of NIEHS.

A full list of all Environmental Health Criteria series titles can be found on the WHO website (www.who.int/ipcs)

The influence of the EHC series did not stop with publication. The intention in producing the EHC documents had, as indicated in the preceding paragraph, always included an applied dimension; many formed the basis for training activities to enhance understanding at national and sub-national level - particularly in developing countries - of chemical safety issues and emergency preparedness in the event of a chemical accident. As Dr Michel Mercier, Director of IPCS through the 1990s, put it, "We have to ensure that the documents are properly used in countries. We want to help countries create their own infrastructure, and train people in how to assess chemicals and translate the results into decisions." (EHP Vol.106:4, 1998.) Training seminars adapted to the specific needs of each country were therefore a key component of the production of the EHC series. This training function was also handled through the networks of collaborating experts that comprised a loose coalition throughout the world. IPCS itself functioned in a "train the trainers" capacity, creating networks of local specialists that could bridge the gap between international and local level.

Other normative publications

While the EHC series was the most authoritative and best known of IPCS's many publications, other categories exist that served different audiences. The Concise International Chemical Assessment Documents (CICADs), like the EHCs, had a normative function. These assessments consist of a summary of the relevant scientific data considered critical for characterization of the risks posed by various chemicals. Based on core national or regional evaluation documents, each CICAD undergoes an international peer-review process, as well as gaining the "stamp of approval" of the CICAD Final Review Board, to ensure the validity of content and conclusions. This is an ongoing process, with a total of 77 CICADs currently available from WHO. A progress report showing details of all CICADs (including new proposals) can be found on the IPCS web site.

http://www.who.int/ipcs/publications/cicad/progress/en/index.html

Information documents

Performing a more applied function, the Health and Safety Guides succinctly summarize essential information on chemical risks, and incorporate practical advice on medical treatment as well as protective measures. The most 'hands-on' product is the International Chemical Safety Card (ICSC), which provides product identity data as well as health and safety information in a brief, easily readable format. Available in multiple languages, the ICSCs are peer-reviewed.

All these information products contributed to training and capacity building activities, and awareness-raising exercises on chemical safety issues, at country level.

Preparing such a wide range of documentation was at no point an easy process. Achieving the collaboration of dozens of different agencies and individual scientists, each with their own understanding, priorities, terminology, expectations and priorities, was never straightforward. The very difficulties encountered, however, underlined again the necessity of having a cooperative process to highlight and mediate these differences, and provide a much-needed forum for continuous dialogue and consensus building. The process was therefore time-consuming, but an essential learning process for all involved.

Scientific workshops

A number of workshops were co-sponsored by WHO and NIEHS as part of the scientific process. Topics examined included environmental immune toxicology and human health; receptor mediated mechanisms in chemical carcinogenesis; methods to assess the effects of chemicals on the ecosystem; risk assessment for neurobehavioural toxicity; susceptibility to environmental hazards; chemical exposure and food allergies; alternative testing methods; and Toxic Equivalency Factors for PCB-like compounds for humans and wildlife.

II. Approach to research activities

Throughout the period of WHO-NIEHS collaboration, national and international scientific workshops were sponsored on a broad range of current and emerging issues, with a view to setting the agenda for collaborative research work across countries in these areas. An aspect of

considerable interest to both partners, and one of the essential principles of the cooperative agreement from the outset, was to foster collaboration between researchers in developed and developing countries, with WHO's global public health mandate, advisory role to governments, and broad institutional and academic partnerships worldwide, serving as a key factor in advancing this agenda.

Topics that received consistent attention through the research focus of the cooperative agreement included biomarkers, endocrine disruptors and persistent toxic substances, risk assessment methodologies, gene-environment interactions and protection of vulnerable populations, such as children.

Throughout the collaboration, a consistent approach to research activities was adopted. The initial step consisted of a core group of WHO/NIEHS staff and national experts identifying and prioritizing the issues and topics that should be advanced through research activities. The extent to which a research agenda could be implemented, however, depended on the programme's capacity to locate funding sources and partners to complement what could be made available through the Agreement. Participation in broad international and regional initiatives was therefore essential to network and identify interested and suitable research partners and potential donors. This approach has yielded notable successes, leading to a considerable degree of activity in the Asian, European and Latin American regions.

Activities in Central and Eastern Europe, for example, started on a limited scale in the 1980s, and expanded over time. A series of three conferences in Central and Eastern Europe on Health and Environment provided critical platforms, culminating in decisions to begin collaborative projects following the "common model" (see below). These meetings, held in the Czech Republic, Bratislava, and Romania between 2004 and 2008, together with processes already in place in the European Region, provided a strong basis for collaborative action on topics relevant to the WHO-NIEHS Agreement.

In principle, all priority research areas supported through the Cooperative Agreement aimed at following a similar implementation strategy, namely:

- create an expert advisory group and plan of action
- build/enhance a network of partners and donors

- assess research needs, identifying key concerns, data gaps and requirements, training and capacity building needs
- promote collaborative research through teams of scientists from developed and developing countries.

Through this process, it is intended that collaborative networks and research capacity should be created and strengthened, data generation enhanced, technology transfer accomplished, and strategies for remediation, intervention and public health promotion established.

Overview of collaborative research

An insight into how collaborative research was addressed throughout the history of the Collaborative Agreement can be seen in the Joint NIEHS-WHO Workshop that took place in 2004 in Research Triangle Park, North Carolina, attended by a wide range of scientists from both developed and developing countries.

As indicated above, the need to switch from the chemical-specific or exposure-specific approach that had characterized the earlier years of the Agreement to a broader disease and health outcome orientation had been identified, and was reiterated at this meeting. Henceforth, increased emphasis would be placed on the effects of multimedia, cumulative, and repeated exposures to mixtures of chemicals.

Among its objectives, the 2004 workshop planned to identify key requirements for effective research collaboration (see table below.) These findings would provide the operational basis for how research was planned and promoted though the Agreement. The meeting reviewed the status of various pilot or research planning projects that had been set in motion though two major conferences on children's environmental health, held in 2002 and 2003 in Thailand. Details of these conferences are given in the following section. These pilot projects addressed:

i) arsenic exposure in pregnant women and children; a preliminary study in southern Thailand measured levels of arsenic in soil, well water, and the toenails of pregnant women, to establish exposure levels. Cord blood samples and urinary specimens from mothers and newborns were also collected.

ii) a cohort study of asthma among Indian children, with the aim of collecting prospective, longitudinal data in different regions of India

to determine how interaction with environmental exposures affects the development of the immune system in early life.

iii) levels of pesticides and persistent organic pollutants (POPs) found in children; to monitor data on levels of POPs and pesticides in children, a proposal was made to designate a series of existing laboratories throughout a number of Asian countries to serve as regional resources for analysis of POPs. Training and funding were being sought to pursue this investigation.

iv) toxicogenomic biomarkers of benzene exposure; the intention was to develop robust biomarkers of exposure to benzene, with a long-term goal of identifying genomic fingerprints of benzene exposure initially in rodents, and subsequently in humans. At the time of this meeting, technology transfer to Thailand was being undertaken.

v) feasibility of national-level longitudinal cohort studies of children's environmental health in developing countries. Four planning consultations were held to explore this issue. The first consultation was in Glion, Montreux Switzerland (October 2003), the second was in Washington, DC, (August 2004), the third was hosted by the Ministry of Health, Mexico in Cuernavaca (November 2004), and the fourth consultation took place in August 2005 in Bangkok, Thailand. In 2009 WHO and Professor Jean Golding published a "A Guide to Undertaking a Birth Cohort Study: Purposes, Pitfalls and Practicalities". This guide was presented at the WHO 3rd International Conference on Children's Environmental Health (June 2009) in Busan, Republic of Korea and participants at this event recommended convening a meeting with experts in industrialized and developing countries involved in longitudinal cohort studies and developing harmonized data collection instruments.

Key Requirements for Successful Research Collaboration Identified at the 2004 WHO-NIEHS Joint Workshop on Collaborative Research between Scientists in Developed and Developing Countries
Strong personal commitment of all collaborators
Equality/mutual respect of all members of the research team
Research topic should be of mutual priority and of benefit to the population studied
Understanding of local customs, regulations, terminology
Personal presence of western scientists, but negotiation with local officials through local scientists
Extend areas of scientific expertise in a synergistic and complementary manner
Ensure research facility has appropriate equipment, trained personnel, harmonized protocols, and quality assurance procedures
Research is supportive of long-term gains, transcending limits of specific research projects (i.e. capable of training, capacity building and technology transfer)
Utilization of train the trainer approaches

III. Children's Environmental Health: planning, research, and raising awareness to global level

As stated above, Children's Environmental Health (CEH) was a significant research topic addressed under the collaborative agreement between WHO and NIEHS. Some highlights of the process are outlined below.

Initial impetus came with the establishment in 1999 of a WHO-NIEHS Task Force on Children's Environmental Health, and an expert advisory meeting at WHO in 2000. This led to the development of a strategic plan and identification of priorities for activities focusing on the environmentally-induced diseases of childhood that produce the heaviest global burden of disease.

International Conferences on Children's Environmental Health: Bangkok, Buenos Aires, Busan

Three further major conferences were held to raise the profile of the topic and gather momentum for a plan of work.

The first was the International Conference on Environmental Threats to Children held in Bangkok in 2002, with a subsequent follow-up workshop held in Pattaya, Thailand, in 2003. The Bangkok conference – the first of three co-sponsored *inter alia* by WHO and NIEHS in different parts of the world - examined the latest data on children's vulnerability to environmental hazards, and the policy measures needed. The conference

output, known as the "Bangkok Statement," proposed a global alliance committed to work together at national and international level to protect and promote children's environmental health.

The follow-up workshop on Healthy Environments for Children in Pattaya focused on the need for collaborative research in the areas identified as priorities at the Bangkok Conference. This generated the pilot collaborative work in the South-east Asian and Western Pacific Regions outlined in the preceding section, and led to the designation of a WHO Collaborating Centre on Children's Environmental Health in Perth, Australia.

The Second International Conference was held in Argentina in 2006, with the aim of identifying regional priorities and laying down an initial research program. The Third International Conference on Environmental Threats to Children, took place in 2009 in Busan, Republic of Korea. It was aimed at furthering recognition of children's environmental health needs, providing a platform for the exchange of scientific experience, learning about and sharing research efforts, and promoting protective policies. The Busan conference brought together participants from 60 countries, as well as 30 organizations. Dr Bill Suk, Director, Center for Risk and Integrated Sciences at NIEHS, underlined the need for effective tools and technologies to assess children's environmental health and stressed the need for coordinated research efforts, harmonization and validation of data collection methods. He pointed out that more understanding was required of the relationship between genetics, infectious disease and environment. In this quest it was anticipated that the WHO Collaborating Centres would play a key role in enhancing present understanding. (Full conference report www.who.int/ipcs/3ceh_report1.pdf)

The Busan Pledge for Action on Children's Environmental Health grew out of the findings and commitments of the two preceding international conferences, in additional to the Busan Conference itself. The Pledge serves as an imperative for international collaboration on research-to-policy action in respect of children's environmental health. The Pledge outlined requirements for effectively addressing children's environmental health and invites all major stakeholders to embark on appropriate courses of action for healthier environments for children. Summarizing the outputs of more than a decade of effort, this pledge serves as a rallying point, background and guidance document for other national and international gatherings. Key among its provisions was a call for a global action plan on children's environmental health.

Based on the Busan Conference and Pledge, a new global action plan on children's environmental health was prepared. This action plan, as well as the Busan Pledge, can be found on the WHO website (www.who.int/ceh). The Pledge was used as a background and consultative document for other events, such as the Fifth Ministerial Conference on Environment and Health held in Parma, Italy in 2010, which focused on child health in a changing world.

Both within the structure of the main conferences, as well as in specific side-events, presentations and side-events were made in which selected priority issues from the WHO-NIEHS Cooperative Agreement were discussed and furthered, taking advantage of the presence of a wide range of experts from many countries for networking, partnership and fund-raising purposes. A side-event organized at the 2009 Busan Conference explored the linkages between environmental risk factors, fetal programming and the early origins of disease.

Children's Environmental Health geographic coverage

The WHO-NIEHS collaboration established a visible level of activity on CEH in three regions. Those in Asia and Europe are referred to above. The same approach has been taken in Latin American countries, where essential partnerships have been formed, and environmental assessments of major threats to children's health undertaken. A number of significant meetings have been held to identify critical research, raise awareness, and forge partnerships for action. Following a meeting in Peru in 2003, the second of the three international conferences co-sponsored by WHO-NIEHS was held in 2005 in Buenos Aires, Argentina. The International Conference on Healthy Environments, Healthy Children: Increasing Knowledge and Taking Action, further identified priority environmental health threats among children, and promoted regional and international collaboration along lines followed in other geographic regions.

Following the Second International Conference on Children's Environmental Health, a workshop was held in 2006 on the Promotion of Collaborative Research in Selected Latin American countries. This workshop identified specific pilot studies intended to catalyse inter-country and regional cooperation and identified a WHO Collaborating Centre for Environmental Health in San Luis Potosi, Mexico.

The research approach defined by WHO-NIEHS was successful in both the Asian and Latin American regions. Much remains to be done in the African region, which has only recently started to prioritize children's health in relation to environmental threats. Participation at the First Inter-Ministerial Conference on Health Security through Health Environments, Libreville, Gabon, in 2008, provided WHO with an opportunity to press for the scaling up of collaboration among African countries, on lines proven in work in other regions. WHO documented the case for a strengthened response to existing and emerging environmental threats, particularly to children, at the second Inter-ministerial Conference on Health and Environment in Luanda, Angola, in November 2010.

IV. Capacity building, training, and information

Measures taken

In addition to the research and research planning/prioritization processes outlined above, WHO and NIEHS have collaborated with a wide range of partners to build capacity and provide information on children's environmental health across many geographic regions. This includes working with the Children's Environmental Health Research Centers in the United States. In addition to co-sponsoring meetings and training events, WHO has provided specific national level support on request, in keeping with WHO's advisory role to government.

Assistance was provided to Senegal in 2008 in response to deaths of children from an outbreak of lead intoxication in Dakar. An international team identified the cause and recommended appropriate preventive action. From the experience gained, an article was published to assist other countries facing continuing hazards from exposure of children to lead (Haefliger P et al. Mass Lead Intoxication from Informal Lead Acid Battery Recycling in Dakar, Senegal. Environmental Health Perspectives 117:1535-1540, 2009). Assistance was also provided to Nigeria in 2010 following a major outbreak of lead poisoning that resulted in the deaths of hundreds of young children in northern Nigeria related to the processing of lead-rich ore for the extraction of gold.

The work of preparing, updating, and disseminating guidance documents to raise awareness of threats to children's environmental health continues. Peer-reviewed documents are being prepared or updated on childhood lead poisoning, mercury exposure, and POPs, aimed at health care providers

and environmental health officers. The popular 2002 booklet prepared in partnership with UNEP and UNICEF, "Children in the New Millennium", was updated with a new focus on current research needs.

To advance children's environmental health, the Environmental Health Criteria Document 237, "Principles for Evaluating Health Risks in Children Associated with Exposure to Chemicals" (IPCS, 2006) was summarized in a booklet suitable for a wide audience. This EHC document was also used as the basis for developing training materials, and as a tool in training seminars and workshops.

V. Longstanding Activities addressed in the Cooperative Agreement

Among the activities identified as of high priority to both NIEHS and WHO during the term of the cooperative agreement, and which have not so far been discussed, is work on endocrine disruptors; toxicogenomics and biomarkers: and integrated risk assessment methods. Below is a brief indication of past or ongoing work in these areas.

Endocrine disrupting chemicals (EDCs)

Concerns expressed by global leaders culminated in the adoption of a resolution by the World Health Assembly in 1997, requesting WHO to take the leadership in undertaking risk assessment as a basis for addressing this emerging problem, including promoting and coordinating research on endocrine-related health effects of exposure to chemicals. This led to the preparation of the *Global Assessment of the State-of-the-Science of Endocrine Disrupting Chemicals*, published in 2002. A measure of its success is its use by many universities as an academic textbook.

This groundbreaking assessment developed a new "Weight-of-Evidence" (WoE) framework, utilizing objective criteria to evaluate causality between exposure to EDCs and particular health outcomes. This framework has been presented at a number of international and national scientific conferences and has been adopted by a number of organizations. At that time, there were no international criteria and guidelines on application of this approach; work is therefore ongoing to elaborate appropriate principles and methods for assessing weight-of-evidence approaches in a variety of complex toxicological issues besides that of EDC. Further information on how the WoE framework is being developed and applied is given in the Appendix.

Concomitantly with the preparation of the 2002 Global Assessment, WHO coordinated the preparation of an inventory of existing global research on the subject, aimed at identifying strengths and weaknesses, and assisting the direction of further work.

Toxicogenomics/biomarkers

There is an important role for the rapidly evolving "-omic" sciences and their accompanying tools in many aspects of toxicology and risk assessment methodologies. Under the aegis of the NIEHS-WHO Cooperative Agreement, several workshops and informal consultations have taken place in recent years. These have focused on reviewing ongoing national and international activities in this area, with a view to planning further work in this area. Noteworthy in this respect are the 2004 International Conference on Biomarkers for Toxicology and Molecular Epidemiology held in Atlanta, Georgia, USA, focusing on how the "-omic" technologies could be used to develop better biomarkers of exposure and susceptibility, and a workshop that same year held by WHO-NIEHS in collaboration with the Princess Chulabhorn International Science Congress on Evolving Genetics and its Global Impact. These consultative processes drew more widespread attention to the issue.

The use and validation of new biomarkers, including those generated by the "-omics" technologies, was examined at a meeting in Brazil in 2008. A publication emerged from this meeting, prepared by SAC members, NIEHS and WHO staff and others, entitled "Ethical issues in measuring biomarkers in children's environmental health," and was published in Environmental Health Perspectives in 2009. (Sly PD et al, 2009. EHP 117:1185-1190).

Biomarkers of benzene exposure and benzene/cancer links

Advances in the use of biomarkers in children were the topic of a dedicated workshop held in the context of the Second International Conference on CEH, Buenos Aires, 2005. Among its purposes was to review the most recent scientific data and technologies on biomarkers of exposure, susceptibility, and effect; to demonstrate the importance of using a life-stage approach in developing biomarkers for use in children; and to promote international research networks and partnerships to address the use of biomarkers among children. Outcomes included identification of a number of priority research areas, and potential scientific partnerships.

(Programme and abstracts are on the WHO website (www.who.int/ipcs/features/biomarkers/en/).

Integrated Risk Assessment

One of the trademarks of WHO's work has been the development of international consensus documents on the scientific principles underlying the improvement of risk assessment methodologies. Over the last decade it has become clear that measures to assess risk need to be addressed in an integrated fashion, reflecting the multiple and combined chemical exposures experienced by humans, animals, and natural resources.

Integrated risk assessment is defined as "a science-based approach that combines the process of risk estimation for humans, biota, and natural resources in one assessment." In collaboration with other international and national organizations, a generic framework was developed to foster integrated approaches to human and ecological risk assessment procedures. The framework, with illustrative case studies demonstrating the value of applying it, was published in a special issue of the Human and Ecological Risk Assessment journal (HERA, Special Issue: Vol.9(1):267-386, 2003).

WHO and NIEHS continue to participate in a wide variety of international meetings worldwide aimed at furthering understanding of risk assessment methods in the light of expanding knowledge, and building consensus in the area.

Toxicogenomics in Risk Assessment

WHO has for a number of years worked with the Organisation for Economic Cooperation and Development (OECD) on toxicogenomics in risk assessment. A Joint WHO/OECD Advisory Group was formed to develop workplans, and WHO played a role in evaluating the validity and reliability of toxicogenomic tools in the development of improved biomarkers. In 2008, the Advisory Group evaluated a number of projects and expected outcomes, as well as future steps, within the framework of the Molecular Screening Project and New Biomarkers Project.

More recently, a Risk Assessment workshop held in 2009 for all those involved in OECD expert groups considered the implications of systematic evaluation of modes of action for dose-response extrapolation in risk characterization, as well as implications for toxicity testing in relation to OECD Test Guidelines. The results were further discussed at the OECD

Joint Meeting held in February 2010. This partnership is therefore set to continue in years to come, and to play a significant role in shaping the future of this evolving area.

VI. New and emerging partnerships

WHO Collaborating Centres

Using the skills and capacities of leading scientific institutions worldwide has always been one of WHO's strategies in delivering its global mandate in all health areas. WHO has now designated five Collaborating Centres in the area of children's environmental health, building on existing successful partnerships, with a view to furthering the research and capacity-building activities planned through the NIEHS/WHO Cooperative Agreement.

These Collaborating Centres include:

- WHO Collaborating Centre for Research on Children's Environmental Health, Perth, Australia. Director: Professor Peter Sly
- WHO Collaborating Centre on Health Risk Assessment and Children's Environmental Health, San Luis Potosí, Mexico. Director: Dr Fernando Diaz-Barriga
- WHO Collaborating Centre for Capacity Building and Research in Environmental Health Science and Toxicology, Bangkok, Thailand. Director: Professor HRH Princess Chulabhorn Mahidol; Professor Dr Khunying Mathuros Ruchirawat
- WHO Collaborating Centre in Children's Environmental Health and Human Environmental Toxicology, Montevideo, Uruguay. Director: Dr Amalia Laborde
- WHO Collaborating Centre on Children's Environmental Health, Mount Sinai Medical Center, New York, USA. Director: Dr Philip Landrigan.

The first meeting of the Network of WHO Collaborating Centres in Children's Environmental Health was held in 2010. The Network of Collaborating Centres provides a solid range of expertise and institutional support to enable a wide range of topics relevant to the WHO-NIEHS Cooperative Agreement to be carried forward. In this way there is an effective structure in place to advance current and future work.

Other opportunities are offered through the relatively new Euro-Asian Association for Children's Environmental Health, created following two regional meetings on wider environmental issues in Kazakhstan in 2005 and 2006 respectively. The Association covers many key countries spanning the Middle East and Central Asia, including Russia and Pakistan, providing rich potential for networking and promoting future collaborative research.

Work in progress

Preliminary or pilot work is now ongoing, under the auspices of the WHO-NIEHS collaboration, in the following areas:

- arsenic in pregnant women in children (South-East Asia, USA, potentially Chile)
- Cohort study on asthma in children (India, Australia, USA)
- Establishing the basis for international long-term cohort studies on children's health and the environment in developing countries (Asian, Central and Latin American countries).
- Biomonitoring of persistent toxic substances (PTSs) and POPs in children (Central and Latin American countries, Canada, USA)
- Biomarkers of polycyclic aromatic hydrocarbon (PAH) exposure (Czech Republic, Thailand).

These topics continue to be addressed in appropriate national and international conferences, workshops and other fora, seeking optimum ways to proceed further and the identification of new research partners and donors. New initiatives are under discussion in other countries.

VII. Future directions

Through the period of collaboration between WHO and NIEHS, it was understood that aside from specific areas of activity covered by the cooperative agreement, much greater ground could be covered by the presence of WHO staff at a wide variety of international events. This represented the interests of NIEHS as well as WHO, and ensured that the interests of the former were presented and represented at platforms worldwide where questions of health, environment, and chemical safety were debated. Particularly in the latter years of the Agreement, clear lines

of distinction were less apparent between the work supported specifically through the cooperative agreement, and work related to these issues carried out broadly through WHO. The presence of SAC members at major policy meetings relevant to WHO assisted this gradual broadening of the mandate in a general sense, while retaining a focus on the specific issues financially supported through the cooperative agreement.

Huge potential remains for further development of the topics already under investigation through the WHO-NIEHS Cooperative Agreement, as well as for new directions. Several new areas of joint interest that are actively being explored are the environment and infectious diseases, e-waste and human health, and the fetal determinants of adult diseases.

Persistent problems including lead-related paediatric conditions also deserve increased attention. Further action has been recommended by experts at recent international conferences (Busan 2009 and Perth, 2009). A Global Alliance to Eliminate Lead Paints started in 2010, with the goal of working towards elimination of lead-related paediatric conditions. A new focus on eliminating developmental disabilities among children was outlined at the 1st meeting of the Network of WHO Collaborating Centres on Children's Environmental Health in October 2010, focusing on global leadership in ensuring concrete country-level action are taken to reduce lead and other neurotoxicants in the environments in which children live, learn and play, thus preventing developmental disabilities through healthier environments. This could be achieved by:

1) Providing scientific evidence, technical guidance and experience of best practices to support policy decisions of Member States.
   - Synthesize evidence for the effectiveness of interventions to reduce children's exposure
   - Develop WHO guidelines on blood lead level of action
   - Disseminate case studies of successful implementation
   - Develop WHO Guideline for mining communities addressing the specific question: How far from the mining should children's homes be?
   - Dissemination of recently-published WHO document on childhood lead poisoning
   - Dissemination of recently-published WHO document on children's exposure to mercury compounds

- Dissemination of recently-published WHO document on POPs and children

2) Promoting practical implementation of actions to eliminate lead and mercury, and other contaminants that are linked to developmental disabilities
   - Enhance activities with Global Alliance to Eliminate Lead Paints
   - Develop tools for monitoring and evaluation of mercury levels in children in communities with small scale mining activities (lead and mercury)
   - Document costs, benefits and impact on health of eliminating lead in petrol and mercury in instruments used in health care settings
   - Capacity building
3) Promoting enhanced communication and visibility

Although the scientific publications that have been produced by the cooperative agreement are excellent, most of the publications are not indexed in PubMed and are reportedly difficult to find. A major investment in modern communication modalities is needed, including working with the National Library of Medicine to ensure that all scientific documents produced by WHO are indexed in PubMed, reshaping the WHO website so that it is easily searchable, and working with *Environmental Health Perspectives* to have a regular column on global health issues. Stronger communication ties are also needed outside the health community, for example, with governments and sectors such as transportation, agriculture, and education.

4) Providing training and exchange opportunities

The world must have a trained workforce to address high priority environmental health issues. The future leaders of environmental health will benefit from experience with translating research into policy. WHO could enhance its capacity to utilize interns and fellows, especially those from Collaborating Centres, since they can continue their collaborative work with WHO after completing their internship. WHO also could invite fellows from NIEHS for short periods (6 months to 1 year), especially those with experience in bench research who wish to become more involved with public health policy development.

VIII. Conclusions

Over the span of 30 years, the WHO-NIEHS Agreement has provided the world with a wealth of essential and authoritative publications and information on chemical safety, on which to base national policy, strategy, legislation, norms, and standards.

The importance of this normative and guidance work to environmental and occupational safety at national level cannot be contested, and has without doubt played a major role in keeping people safe and healthy in a wide variety of settings.

Impact of Cooperative Agreement activities

Throughout the Cooperative Agreement period, changes in approach have been needed. From the early days, characterized largely by assessment of risks and problems alone, and a reactive response to crises, a transition has been made to a decision-making and guidance role, and a proactive approach. The establishment of pioneering research and knowledge-gathering initiatives and partnerships points the way to larger-scale activities around which the global scientific community has, and must continue to mobilize, maintaining impetus and ensuring that momentum generated through mechanisms such as major international conferences is not lost.

This change in direction has been further characterized by a shift from a one-risk, disease-specific approach to an integrated and holistic mode of assessment and investigation geared to addressing multiple exposures and complex health outcomes.

In achieving this step-change, the complementary capacities of both partners have worked well. The coordinating role and global reach of WHO in mobilizing experts from all corners of the world has been essential to this process, facilitating the consensus building processes globally necessary for progress in new and complex areas of environmental health and chemical safety work. The financial and technical assistance provided by NIEHS, and the Scientific Advisory Committee guiding the collaborative activities, has enabled WHO to mobilize other stakeholders, increase the willingness of Member States to act in this area, and thereby increase the value of the NIEHS contribution.

The work undertaken through the Agreement has contributed to enhancing global understanding of chemical safety hazards in a rapidly changing world. It has served to cast a spotlight on areas of major global

concern, particularly for vulnerable populations such as children and the poor, organizing initial investigations, and identifying remedial plans and activities. From limited numbers, both in terms of human and financial resources, a vast area of work has been identified and set in motion.

Impetus of Millenium Development Goal Framework

One of the most significant milestones passed in the course of the 30-year WHO-NIEHS Agreement has been the adoption by all nation-states of the Millennium Development Goals (MDGs). The targets are sometimes described as modest, calling as they do in many cases for only the halving of major impediments to global development. However, they represent global consensus on the most important aspects around which international cooperation must coalesce, not only until 2015 but far beyond. Like all environmental components, chemical safety has a major role to play in ensuring that not only the MDG Target on Environmental Sustainability is met, but that it makes an appropriate contribution to the Targets of other MDGs. Appropriate use of chemicals can, for example, boost production and reduce healthcare costs – hence increasing income - while their misuse produces the reverse. Inadequate education, particularly science education, leads to poor monitoring and evaluation of chemical use, and reduced ability to implement international guidance. The MDG health targets benefit greatly from appropriate use of pharmaceuticals, whereas the environment is significantly harmed by chemical pollution of land, air and water. Appropriate control of chemicals is essential to halting and reversing climate change.

For all these reasons, much greater progress is needed. International cooperation must be strengthened and better coordinated if the MDG process beyond 2015 is to function successfully. Key among these needs will be an enhanced focus on national capacity building, calling *inter alia* on the huge amount of information generated through the WHO-NIEHS Cooperative Agreement.

It is hoped that the partnership will continue, building on this exceptional 30-year, intergenerational experience that exemplifies the saying, "From little, much."

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Appendix

Weight of Evidence Framework

Website: http://www.who.int/ipcs/publications/en/ch7.pdf

Brief outline of the Weight of Evidence framework

The framework begins with a clear statement of the hypothesis under examination, which contains two distinct elements. First, the outcome of concern (e.g., a specific human disease or status of an ecological species) is linked to a putative stressor that is acting on the individual or population. Second, exposure to the stressor results in endocrine-mediated events that ultimately result in the outcome of concern. These elements need to be clearly stated in order to evaluate the scientific evidence regarding their potential relationship. The evaluation of the scientific evidence utilizes five aspects: 1) temporality, 2) strength of the association, 3) consistency of the observations, 4) biological plausibility of the effect, and 5) evidence for recovery following diminution of the stressor. The aspect of specificity of the association, a traditional component of causality in the epidemiological setting, is not included in this framework because some of the examined outcomes (e.g., semen quality) are quite apical in nature and influenced by many factors, and the component of biological plausibility covers the linkage between the mechanism of action and the outcome (e.g., estrogen mimics and vitellogenin induction in fish) and hence deals implicitly with specificity.

1) The aspect of temporality explores whether the presumed cause of the outcome of concern preceded the appearance of altered physiological states, rates of disease, or population health. Although information regarding the onset of exposure is often lacking, a few examples are included in which the temporal pattern of exposure precedes the observed effect.

2) The aspect of strength of the association examines a) the incidence rate of the outcome in a population, b) the extent to which other known risk factors may have contributed to this incidence, c) the risk that could be attributed to the exposure of concern, and d) the shape of the dose–response curve as determined either from laboratory or population-based studies.

3) The aspect of consistency of the observations examines how frequently similar or dissimilar conclusions are reached in the literature and discusses any apparent discrepancies. It also evaluates whether results came from multiple geographical areas, whether multiple species would be expected to react in a similar fashion, and whether studies employed similar dosages.

4) The aspect of biological plausibility examines multiple areas of research (e.g., basic aspects of biology, embryology, endocrinology, population dynamics, chemical/physical properties, etc.) that help determine the mechanism of action for the compounds of concern. Consideration of a substance's mechanism is critical because this criterion is central to the overall assessment of whether or not a substance is deemed to be an "endocrine disruptor". In this assessment, a substance meets the operational definition of an endocrine disruptor if it "alters the function of the endocrine system and consequently causes an adverse health effect in an intact organism, or its progeny, or (sub) populations."

5) The aspect of evidence of recovery examines whether the occurrence of the adverse outcome is reversible upon diminishment or cessation of the suspected exposure. When examining the issue of recovery, it is important to note that some effects may be developmentally imprinted, and hence recovery may only occur in subsequent generations, or may even express themselves in subsequent generations that have not in themselves been exposed to the stressor.

Overall Strength of Evidence

The final part of the framework, overall strength of evidence, makes an evaluation regarding the relationship between an outcome of concern and exposure to a substance and whether or not these associations involve endocrine-mediated mechanisms.

Dr David P. Rall,
NIEHS Director (1971-1990)

Dr Thressa Damstra,
Scientific Officer, WHO
(Principal Investigator 1997- 2007)

Dr Jenny Pronczuk,
Medical Officer, WHO
(Principal Investigator 2007 - 2009)

IPCS staff (1992)

IPCS Staff Front row: Mme H. Leblanc, Mrs A. Massy, Miss A. Catania, Mme G. Grand-Maison, Mr K. Uchida, Mme J. Duménil, Mrs H. Yasandikusuma, Mrs E. Ephraim, Miss T. Mawer
Second row: Mr D. Schutz, Dr C. Moreau, Mrs L. Akkerman, Dr B.H. Chen, Dr H. Galal-Gorchev, Miss H. Palmer, Miss E. Burt, Dr M. Mercier, Dr J. Haines, Dr J. Pronczuk de Garbino
Back row: Mrs P. Bartocci, Dr K. Jager, Dr P. Jenkins, Mr X. Lourduraj, Dr R. Plestina, Dr M.Gilbert, Dr E. Smith, Dr J. Herrman, Dr G. Becking

Mrs. Kathy Prout, administrative assistant, IRRU, 1989