# The Importance of International Co-operation and Team Working

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International cooperation and team working are required to address complicated environmental health impact issues of global importance or those which may be multi-causal in nature and affect different groups of populations. Cancer is a good example to illustrate the complexity of such issues through its complicated etiology and, for certain types, unique geographical distribution.

It is well understood that carcinogenesis is multi-stage and multi-causal in nature. Thus, a multidisciplinary approach is required to identify etiological factors and the mechanisms involved. A series of successful studies of liver cancer, from identification of causal factors and the mechanisms underlying carcinogenesis that led to the discovery of biomarkers of exposure and early biological effects and eventually development of preventive measures (Kensler et al 2011), underscores the need for international cooperation and team working.

For successful research/scientific collaborations, certain requirements must be met. First, the partners in the developing countries require an infrastructure that is sufficient and appropriate to support the collaboration. This includes well-designed laboratories, up-to-date and well-maintained equipment, and, importantly, qualified staff with the know-how to undertake research and put the technology transfer to immediate use. A second important aspect is networking. Partner institutions with pre-existing national and regional networks of cooperation would allow for expansion of the collaboration with the expert institution from a developed country from a bilateral one to a regional one through the multiplying effect. Third, the local partner should have funds available to undertake research activities as part of its main function, such that the activities involved in the collaboration are simply an extension of on-going activities as opposed to completely new undertakings.

The Chulabhorn Research Institute (CRI) has undertaken an international collaborative research project on the study of arsenic exposure *in utero* and potential effects on gene expression, with implications on the future health of the developing fetus after birth and beyond. This project was conceived at the Asia-Pacific regional workshop on Children's Environmental Health organized by WHO, the US NIEHS and CRI in 2002 based on the problem of arsenic exposure in the region that affects millions of people and the interest in gene-environment interactions. At that time CRI had limited experience in the technology involved in the study of gene expression and analysis of the results. Collaboration with international experts at MIT with support from the US NIEHS made it possible to complete the first Thai study that showed that arsenic exposure *in utero* resulted in gene expression changes with a set of 11 genes associated with prenatal arsenic exposure that could be associated with disease development, such as cancer, later in life (Fry et al 2007). Epidemiological studies in Antofagasta, Chile, had shown that arsenic exposure during early life was associated with cancer incidence in young adults (Naujokas et al 2013). Further studies in the same Thai cohort revealed both epigenetic changes, as well as genotoxic damage, occurring as a result of arsenic exposure *in utero* that persisted throughout childhood (Hinhumpatch et al 2013; Phookphan et al 2017).

The key findings of the study were validated in other populations in Vietnam in which arsenic contamination of ground water poses a serious problem. The collaboration between Thailand and Vietnam was possible through pre-existing collaborations between CRI and the Vietnamese National Institute of Occupational and Environmental Health, who were also interested in studying health effects in populations in the country exposed to arsenic through contaminated ground water. Expanded collaborations also included Columbia University, which had conducted extensive research in this field in Bangladesh, and Gwangju Institute of Science and Technology (GIST), the Republic of Korea, with expertise on the geological aspects of arsenic contamination and filtering technologies that could be applied towards risk management. The project, which was funded by the US NIEHS through Columbia University and CRI unveiled a series of changes that helped to explain the mechanisms leading to various genetic changes and damage that may contribute to the elevated cancer incidence previously reported in Chile. This research continues today, where a 12-year cohort in Thailand is continually monitored for biomarkers of early biological effects or manifestation of health effects that can be associated with exposures *in utero* and in early life. In Vietnam, results from this collaboration led to placement of environmental health monitoring in potentially exposed populations on the national agenda. The ability to compare results in several populations with differences in genetics, behavior and exposure levels helps to validate and refine the gene expression profiles to make them more beneficial and applicable for research towards identifying treatment and prevention options in larger groups of exposed people.

In children, according to the World Health Organization, environmental exposures account for a large percentage of all diseases including cancer, and disproportionately affect children from poorer countries and poor children in all countries. Therefore, in principle, there is an urgent need for international cooperation between developed countries that are more scientifically and technologically advanced and developing countries with prevalence of the disease of interest.

Several important collaborative networks and programmes have been developed to promote international collaborations. The Global Network of WHO Collaborating Centers in Children's Environmental Health was created to address the issue at the local, national and international levels. The Network is comprised of research institutes from around the world to collaborate and share service and expertise among centers. Thus, through the Network, international cooperation can be facilitated and fostered. The Newton Fund, which was initiated in 2014 and is part of the United Kingdom's Official Development Assistance (ODA), aims to use science and innovation partnerships to promote economic development and social welfare in partner countries, who also provide matched resources. Examples of CRI collaborative projects through this fund include a project entitled, "Ultrafine and Submicron Particles in the Urban Environment in Thailand – Size, Concentration, Composition and Health Impacts", which aims to characterize ultrafine particles and the associated chemical species in Bangkok, and a project entitled, "Proline Rich Homeodomain Protein (PRH) in intrahepatic cholangiocarcinoma, disease progression and response to chemotherapeutics", which aims to assess potential new strategies for cancer treatment. One of the key strengths of this programme is the matching of UK expertise with local researchers to create meaningful and lasting partnerships in key research areas of mutual benefit.

International collaborations can help to more effectively address the exposure-disease continuum for a broader array of exposures, resulting in better risk assessment and increased utility of exposure in clinical settings. However, such an undertaking is not simple, and requires a pre-existing network of collaborations among institutions that not only have the technical expertise and funding, but also the infrastructure and local know how to be able to optimize the chances of success for that collaboration. There is no question that such collaborations are able to maximize the effective sharing of limited resources, thus optimizing the benefits for all concerned.


1. Kensler TW, Roebuck BD, Wogen GN, Groopman JD (2011) Aflatoxin: A 50-year odyssey of mechanistic and translational toxicology. Tox Sci. 120, S28-S48
2. Fry RC, Navasumrit P, Valiathan C, Svensson JP, Hogan BJ, Luo M, Bhattacharya S, Kandjanapa K, Soontararuks S, Nookabkaew S, Mahidol C, Ruchirawat M, Samson LD (2007) Activation of inflammation/NF-kappaB signalling in infants born to arsenic-exposed mothers. PLoS Genet. 3(11): e207.
3. Naujokas MF, Anderson B, Ahsan H, Aposhian HV, Graziano JH, Thompson C, Suk WA (2013) The broad scope of health effects from chronic arsenic exposure: update on a worldwide public health problem. Environ. Health Perspect. 121(3): 295-302.
4. Hinhumpatch P, Navasumrit P, Chaisatra K, Promvijit J, Mahidol C, Ruchirawat M (2013) Oxidative DNA damage and repair in children exposed to low levels of arsenic in utero and during early childhood: Application of salivary and urinary biomarkers. Toxicol Appl Pharmacol. 273:569-579.
5. Phookphan P, Navasumrit P, Waraprasit S, Promvijit J, Chaisatra K, Ngaotepprutaram T, et al. (2017) Hypomethylation of inflammatory genes (COX2, EGR1, and SOCS3) and increased urinary 8-nitroguanine in arsenic-exposed newborns and children. Toxicol Appl Pharmacol. 316:36-47.