COLLEGIUM RAMAZZINI STATEMENT ON CHEMICALS CONTROL
A Call for Action to Protect Human Health

The European Union (EU) is currently conducting a review of the Registration, Evaluation, Authorisation and Restriction of Chemical substances (REACH) legislation. In the USA, a proposal has recently been made to strengthen current legislation enacted in 1976 that provides undemanding/limited requirements for testing of chemicals. The implication of regulatory systems in US and Europe are huge for the rest of the world, which may often follows what is decided in the global north, since many countries lack the capacity to do their own risk assessments or manage chemicals safely through their own standards. For that reason managing chemicals so as to prevent or limit harmful human and environmental health impacts will have global benefits.

Exposure to toxic chemicals in the places that we work, learn, live, and play can lead to serious adverse health effects, especially in vulnerable populations, such as the elderly, infirmed, and early life stages including fetal, neonatal, and childhood development. Yet we are exposed to hundreds of chemicals from the air we breathe, the water we drink and wash in, the food we eat, the ground we walk and play on, and the consumer products in our homes and workplaces. However most of the chemicals to which we are exposed – including the high-volume production chemicals (produced or used in the US at over a million pounds per year) that make up most of the pollution in our environment [is this true internationally?]- have not been adequately tested for toxicity. International collaboration on chemicals testing and control is therefore an urgent priority.

Because there is such a large number of chemicals to which people routinely come into contact with, detailed test information will not realistically be obtained in the near future for even the most frequent chemical pollutants. Thus, regulators, lawmakers, and companies that manufacture or use chemicals must apply the Precautionary Principle to limit or eliminate uses which could lead to human exposures or environmental releases of untested and potential unsafe chemicals.
To deal with uncertainty with regard to chemical hazards and risks, the World Trade Organization already allows provisional measures "on the basis of available pertinent information", thereby avoiding delays in regulation when the evidence is insufficient for formal risk assessment. Similarly, the EU Treaty includes the precautionary principle, which facilitates protection against plausible health risks in the absence of scientific certainty.

The Collegium Ramazzini urges the USA, the EU, the WTO and other international organizations and governments to use peer reviewed scientific evidence in risk assessment to adopt strong legislation to obtain toxicity test data on industrial chemicals and to protect public health and the environment from unsafe chemical exposures or to untested chemicals.
The Collegium Ramazzini recommends the following:

- Public disclosure of all data and information relevant to evaluating the health and safety of chemicals and conducting risk assessments. Information should be publicly available for scrutiny by governments, workers, and communities.
- Corporate policies that hold chemical suppliers to the health, safety, and environmental standards of performance required/observed in the most regulated countries the corporation operates in; with public disclosure of the identities and locations of the suppliers.
- Policies and incentives to drive global markets towards the use of less-toxic or non-toxic products and processes, particularly targeting for elimination chemicals that are: a) persistent, bioaccumulative, and toxic, or b) very persistent and very bioaccumulative.
- Laws that shift the responsibility from governments to chemical producers and users to support

third-party toxicity testing, risk assessments, and environmental monitoring of chemicals used in industrial processes and commercial products.

- Study selection by government and public health agencies based on academic research, published in respected scientific journals after a peer-review process and publicly accessibly , instead on "Good Laboratory Practices" (GLP) criteria.
- For existing chemicals, restrictions on the expansion or new use of a chemical and default interim health protective standards pending the completion of a risk assessment.
- For existing and new chemicals, require regular monitoring of workplaces, workers, and the general population to identify and prevent unsafe exposures or environmental releases. Data should be publicly available for scrutiny by governments, workers, and communities.

Current safety testing is inadequate

A large majority of industrial chemicals to which workers and consumers are exposed have not been adequately tested for adverse effects on human health. The REACH legislation in the EU constitutes an important advance, as it requires producers and users of an estimated 30,000 chemicals in commerce in Europe to register them and provide information on their production, use, hazard and exposure potential [Will this information be publicly available?]. For chemicals identified as Substances of Very High Concern[1], REACH will allow their use only if explicitly authorized. However, delays have occurred, as the responsible industries have not delivered the information needed in a timely fashion[i].

Additional efforts are being mounted to assess the toxicity of chemicals on the market in a more systematic way. The voluntary High Production Volume (HPV) Chemical Challenge in the U.S. is developing basic screening information on the potential hazards of some 2,000 of the highest-volume chemicals in use. While only slow progress has been made, this effort represents an important, though limited improvement, as the Toxic Substances Control Act (TSCA), the major US law enacted in 1976 to regulate chemicals, allowed the 60,000 chemicals in use at the time to be "grandfathered", i.e., to exempt them from any additional testing.

Canada's Domestic Substances List (DSL) Categorization, mandated by law in 1999, examined for the first time information available on the roughly 23,000 previously unassessed chemicals in current use. More than 4,300 of them were found to warrant further scrutiny of their potential risks[ii].[NEED A REFERENCE HERE]

Despite these initiatives, basic information on the potential toxicity of commonly used chemicals remains very patchy. Further, current toxicity testing is insufficient to identify the risks that affect the population at large. Tests are generally carried out by administering the chemicals to experimental animals during adolescence, and then toxicological endpoints are examined that may include acute toxic effects such as weight loss, organ weight changes, and gross morphology or chronic effects such as cancer. Further testing will be needed to identify biologically significant effects such as disruption of immune or endocrine functions, low dose effects, effects from early life-stage exposures, non-monotonic effects, or behavioral and cognitive effects that are often missed with traditional toxicity testing[iii].

As early as the 1980s, the ability of animal studies to predict human risks was established and animal

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[1] Certain substances that may have serious and often irreversible effects on human health and the environment can be identified as Substances of Very High Concern (SVHCs). A Member State, or ECHA on request of the European Commission, can propose a substance to be identified as an SVHC.

data used by regulatory agencies worldwide to set human exposure limits for hazardous materials[iv][v]. Current OECD guidelines for chronic toxicity/carcinogenicity studies start the exposure in young adult and stop them after 2 years, which correspond to 2/3 of the lifespan, in human-equivalent terms to about 60 years of age. We know that 80% of all malignant tumors arise, both in rats and humans, after this age, and different degenerative environmental diseases also manifest later in life, so we are missing a lot of information by limiting animal tests to less than a full life-time. With appropriate protocols experimental studies can: (1) make a decisive contribution to risk assessment; (2) offer viable prospects for predicting the existence of potential long term risks from hazardous agents; 3) assess the hazards of low doses of chemicals, chemical mixtures, exposures during early life stages, and other real-world exposure scenarios.[vi]

Government and public health agencies should not rely on GLP studies - "Good Laboratory Practices" (GLP) standards were imposed on industry labs during the 1970's after flagrant violations and fraud were identified.[vii] GLP requirements are designed to set a baseline of cleanliness, animal care, and record-keeping; they are not associated with higher quality research, proper study design or correct statistical analysis. However, study designs are often very outdated and do not reflect the current science, most sensitive disease endpoints, or chronic disease outcomes. In contrast, academic research has been published in respected scientific journals and relies on the peer-review process and public accessibility to uphold scientific quality. Over thirty environmental health experts have published a scientific perspective on why government and public health agencies should not use "Good Laboratory Practices" (GLP) criteria for study selection.[viii]

Early danger signals have been overlooked

Many classic technologies were initially hailed as beneficial and safe, but later found to cause harm. Best documented are lead-containing additives used in paint and petrol, asbestos, polychlorinated biphenyls (PCBs), and the ozone-destroying chlorofluorocarbons (CFCs)[ix]. A recurrent theme in each of those episodes was that commercial introduction and wide dissemination of the new technology preceded any systematic effort to assess potential toxicity. As evidence emerged that occupational and environmental exposures were causing adverse effects on human health, vested commercial interests actively opposed efforts to examine and control exposures to these materials. Industries involved have used highly sophisticated disinformation campaigns to confuse the public, and they have directly attacked the scientists who called attention to the risks[x].

These examples of missed early warnings underline a major dilemma of current risk assessment, where uncertainty rarely triggers stricter protection and most often is used as an excuse not to regulate at all. Thus, early warnings still tend to be ignored and not acted upon, while we are waiting for evidence to accumulate to a "convincing amount", which may require many decades. At the same time, no concerted effort is made to obtain the missing information to inform the risk assessment.

For decades most chemicals have been presumed to be safe in the absence of clear evidence of harm. Regulatory agencies had to effectively prove beyond reasonable doubt that a chemical posed a risk before it could take any action to restrict its production or use. This passive approach provided little or no incentive for companies to submit or develop risk information since it may thereby triggering new limitations on its use. As a result, efforts to control exposures and to prevent injury have often been delayed, sometimes for decades.[xi]

For a few substances (such as pharmaceuticals and pesticides) the approach, while imperfect, did require more risk information (toxicity testing and exposure data) than for industrial chemicals. For these

products, producers had the burden of providing information to government deemed sufficient to evaluate risks, at least when used as intended.[xii]

Outdated legislation - US

Because chemical pollution does not respect national borders, and because chemicals production and commerce are international, legal solutions must be found on an international scale.

The Toxic Substances Control Act (TSCA), the major US law enacted in 1976 to regulate chemicals is terribly flawed, making it nearly impossible for the US Environmental Protection Agency (EPA) to take action to protect the public from even the most dangerous chemicals. At the time it was enacted, 60,000 chemicals were available for use in commerce, and all of these chemicals were "grandfathered" under the law – allowing them to continue to be used, without any additional testing or meeting of a safety standard. Another problem was requiring EPA to prove that a chemical was harmful before being able to restrict its use. In the 30-plus lifespan of TSCA, the EPA has required testing of only about 200 chemicals, and established limited restrictions on some uses of only five (PCBs, chlorofluorocarbons, dioxin, asbestos, hexavalent chromium). For EPA to be able to take action to regulate use of a chemical under TSCA, the agency must demonstrate that the chemical presents or will present (not "may present") an unreasonable risk of injury to public health or the environment. But there is no requirement or deadline under TSCA for EPA to complete assessments of chemicals, and no regulatory consequences if EPA fails to complete the assessment. This has lead to delays of years or even decades in completing chemical assessments, and invites political and industry interference in the process. These central features of TSCA place the burden on the EPA to prove harm, and both incentivize and reward efforts by chemical manufacturers and users to prevent EPA from making any negative determinations about their chemical products.

For EPA to be able to take action to regulate use of a chemical under TSCA, the agency must demonstrate that the chemical presents or will present an unreasonable risk of injury to public health or the environment. Delays of years or even decades have occurred, as there is no deadline for completion of such risk assessments of chemicals. Although required by the law, manufacturers have provided little or no information on the potential health or environmental impacts of most chemical products. In addition, much of the information submitted is designated as confidential and must therefore be withheld from the public and even from state governments. While there are criminal penalties for knowingly not disclosing such information, there are no penalties for making false safety claims, thus again providing a disincentive against submitting even the most basic information, such as how much of the chemical is being produced.

Information shielded from the public

Of the approximately 22 thousand chemicals commercialized under TSCA, manufacturers have provided little or no information on the potential health or environmental impacts. And, much of the information provided is designated as Confidential Business Information (CBI), and therefore withheld from the public and even from state or foreign governments. While there are criminal penalties for knowingly disclosing CBI information, there are no penalties for making false CBI claims, thus incentivizing broad CBI claims for even the most basic information such as where the chemical is manufactured, the name of the company that makes the chemical, or how much of the chemical is being made. Although health and safety data is not supposed to be withheld under CBI, in practice EPA has allowed the identity of the chemical to be CBI-protected so the public has no way of knowing what chemical the data refers to. In May 2010 US EPA announced its intention to review future CBI claims for health and safety data

submissions, and to deny CBI claims for the chemical identity, providing the possibility for some small measure of progress towards public transparency and accountability.

Following the chemical disaster in Bhopal, major global chemical corporations adopted corporate policy statements to the effect that they observe uniform standards of worker and environmental protection, worldwide. That is, they accepted the responsibility in the late 1980s to control hazards to human health from their operations, even in the least regulated countries. But in recent decades, hazardous production that used to be managed by subsidiaries of the chemical giants has been outsourced to wholly separate companies. These supplier companies operate in China and other countries where free trade unions, independent media, environmental non-governmental organizations, government regulation, and liability are minimal or non-existent. Chemical and microelectronics corporations, unlike some clothing and footwear corporations, have not adopted policies of taking responsibility for these firms manufacturing materials for their global enterprises -- or even publicly disclosing the identities of their suppliers. [xiii]

Need for accountability and disclosure

Global corporations are morally and ethically responsible for all the economic activities that they place in motion, regardless of whether these activities are conducted by their subsidiaries or by separate corporate entities. As acknowledged by many global chemical enterprises, there is no justification for international "double standards" in health, safety and environmental protection. Global corporations should accept responsibility for assuring that, worldwide, the activities of their suppliers are up to the standards of performance they would achieve in their own activities in the most regulated countries. And to demonstrate their good faith in accepting this responsibility, they should publicly disclose the identities and locations of their suppliers.

The challenge

Workers are exposed to chemical substances/agents, of which only a few hundred are regulated, and surveillance efforts are not aimed at identifying or preventing adverse health effects that may develop after several years of employment. The general population is also at elevated risk. Following initial enthusiasm about genetic causes of disease, a recent estimate suggests that only 10 % of the burden of disease can be explained by genetic factors[xiv], thus leaving about 90% to be attributed to environmental factors. Using current routine methods, the U.S. Centers for Disease Control and Prevention can reliably identify more than 200 industrial chemicals in blood and urine samples from the general population[xv]. Similar efforts to document exposure to chemicals exist in many countries in Europe. Most of these substances are thought to pass the placenta or to be excreted in milk, so that a mother shares her chemical burden with her child, who at the same times undergoes crucial development that is highly vulnerable to toxic damage.[xvi]

With regard to children alone, information on the costs to society attributable to the best known pollutants suggests annual expenses to society due to toxic effects are in excess of $50 billion in the US.[xvii] Costs to society due to effects in adults, such as cancer, cardiovascular disease, obesity, and other adverse effects add substantially to the costs, although no estimates are available. Highly-exposed workers constitute a particular risk group, which carries a high burden of chemically-induced disease. Additional costs carried by patients and families are often regarded as intangible, but should not be ignored. Transgenerational effects pose an even more ominous risk.

Existing mechanisms

Mechanisms already exist for chemical control and protection of vulnerable population against exposure to chemicals. To deal with uncertainty with regard to chemical hazard/risks, the World Trade Organization (WTO) Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement) from 1995 allows provisional measures "on the basis of available pertinent information". It thereby avoids major delays in regulation when the evidence is insufficient to allow formal risk assessment.

In 1996, passage of the US Food Quality Protection Act (FQPA) amended the US EPA's authority to regulate pesticides by requiring EPA to ensure that there is a "reasonable certainty that no harm will result" from dietary and certain other exposures to pesticide chemical residues, to account for the particular susceptibilities of and provide special safeguards for infants and children, and to take into account available information concerning exposure levels from the aggregate of uses of a single pesticide and the cumulative exposure to related pesticides. The result was cancellation of most of the organophosphate pesticides, deemed the most hazardous class of pesticides, from residential uses and uses on foods that kids commonly consume. However, their use continues in agriculture, where farm families, farmworkers including children and young adults, and neighbouring communities continue to be exposed.

The EU Treaty includes the precautionary principle, which facilitates protection against plausible health hazard/risks in the absence of scientific proof. However, although the framework therefore exists for prudent decisions under uncertainty, the necessary countermeasures have not emerged to make up for the impasse due to the existing delays in chemicals testing and risk assessment. [xii] In general, the precautionary[xviii] principle incorporates the necessary elements to form the bedrock of a new framework.

Need for precaution

A new paradigm is needed to provide the necessary support for public health and investment in safe chemical use in the future. The major challenge is to secure that at least temporary decisions can be made in the absence of clear scientific documentation.

The key element of the precautionary principle is that it provides justification for acting in the face of uncertainty, as a tool for acting on the basis of early warnings. Under the precautionary principle, the burden of proof should therefore be shifted. Accordingly, technologies are no longer presumed safe simply because evidence of risk is unavailable.

Instead, safety must be documented. Existing chemical production and usage must require scrutiny to determine the need for safeguards, and all new technologies should be properly examined for potential toxicity before commercial introduction.

Accordingly, the review of the REACH legislation must consider a new framework, where the approach is shifted to secure safety, rather than to detect risk. Thus, decisions should be based on hazard assessment that focuses on possible adverse effects on the most vulnerable population. This approach will require new test methods that assess the adverse effects during early development, such as endocrine disruption, neurotoxicity, and immunotoxicity and the development of reliable testing strategies for newly emerging risks like those linked with the increasing use of nanomaterials. Alos, he results of peer reviewed science should be taken into consideration – not only the results of 'regulatory science' which is outdated and not adequately sensitive.

In the U.S., the proposed Child Safe Chemical Act requires: that new chemicals be tested and found safe

for children before they are brought to market; that manufacturers prove the safety of the 62,000 chemicals "grandfathered in" without testing under TSCA thirty years ago, if these chemicals are to remain in commerce; that the U.S.EPA develops a list of "priority" chemicals that will receive immediate attention; and that all of this information be regularly updated and made publicly available. This initiative is an important step in the right direction to secure chemical safety internationally.

Need for research

Progress in chemicals control and disease prevention will require research to understand better the risks and how they may be combatted. In the absence of incentives to study high-priority chemicals, much of the current academic research on environmental chemicals has focused on well-known hazards.[xix] Mechanisms are needed to inspire and support science that will help risk assessments for hazards that are poorly understood and therefore need exploration to inform prevention efforts.

In more general terms, new issues in toxicology and environmental science need attention, especially the existence of low-dose toxicity that has been demonstrated for several industrial chemicals much below levels that were thought to be safe. The increased vulnerability during early development needs to be examined in greater detail, how it relates to different organ systems and the long-term consequences. Further, the so- called cocktail effect due to exposure to multiple contaminants needs to be taken into consideration. [xx] [xxi]Some of these questions can be addressed in experimental studies, but others will require prospective population studies, such as the US National Children's Study and related efforts in the EU and elsewhere.

While support for targeted research on these issues is a high priority, such investment should not be used as an excuse to delay necessary decisions on chemicals control. Such decisions will always remain temporary and will be subject to possible adjustment as new information emerges. It will be a tragic mistake to continue delaying prevention in the hope that science will soon provide complete guidance on how to protect human health.

About the Collegium Ramazzini

The Collegium Ramazzini is an international scientific society that examines critical issues in occupational and environmental medicine with a view towards action to prevent disease and promote health. The Collegium is dedicated to the prevention of disease and the promotion of health. The Collegium derives its name from Bernardino Ramazzini, the father of occupational medicine, a professor of medicine of the Universities of Modena and Padua in the late 1600s and the early 1700s. The Collegium is comprised of 180 physicians and scientists from 35 countries, each of whom is elected to membership. The Collegium is independent of commercial interests.

REFERENCES

[i] Gilbert N. Data gaps threaten chemical safety law. Nature. 2011; **475(7355):** 150-1.

[ii] Canada (...)

[iii] Barouki R, Gluckman PD, Grandjean P, Hanson M, Heindel JJ. Developmental origins of non-communicable disease: implications for research and public health. Environ Health. 2012; **11:** 42.

[iv] Huff J. Long-term chemical carcinogenesis bioassays predict human cancer hazards. Issues, controversies, and uncertainties. Ann NY Acad Sci. 1999; 895: 56-79.

[v] International Agency for Research on Cancer (IARC). IARC Monograph Supplement 7. 1987

[vi] Soffritti M, Belpoggi F, Esposti DD, Falcioni L, Bua L. Consequences of exposure to carcinogens beginning during developmental life. Basic Clin Pharmacol Toxicol. 2008; **102(2):** 118-24.

[vii] History of GLP here: http://www.labcompliance.com/tutorial/glp/default.aspx#history

[viii] Myers JP, vom Saal FS, Akingbemi BT, Arizono K, Belcher S, Colborn T, Chahoud I, Crain DA, Farabollini F, Guillette LJ Jr, Hassold T, Ho SM, Hunt PA, Iguchi T,Jobling S, Kanno J, Laufer H, Marcus M, McLachlan JA, Nadal A, Oehlmann J, Olea N, Palanza P, Parmigiani S, Rubin BS, Schoenfelder G, Sonnenschein C, Soto AM,Talsness CE, Taylor JA, Vandenberg LN, Vandenbergh JG, Vogel S, Watson CS,Welshons WV, Zoeller RT. *Why public health agencies cannot depend on good laboratory practices as a criterion for selecting data: the case of bisphenol A*. Environ Health Perspect. 2009 Mar;117(3):309-15.

[ix] European Environment Agency. Late lessons from early warnings: the precautionary principle 1896-2000. Copenhagen; 2001.

[x] 4. 5. Michaels D. Doubt is their product : how industry's assault on science threatens your health. Oxford ; New York: Oxford University Press; 2008.

[xi] Sass JB, Rosenberg D. *The Delay Game: How the industry ducks regulation of the most toxic substances*. A report of the Natural Resources Defence Council. October, 2011

[xii] Denison RA. Not That Innocent: A Comparative Analysis of Canadian, European Union and United States Policies on Industrial Chemicals. Washington, D.C.: Environmental Defense; 2007.

[xiii]B Castleman et al., *Code of Sustainable Practice in Occupational and Environmental Health and Safety for Corporations*" Int J Occup Environ Health 2008; 14:234-235

[xiv] 7. Wild CP. Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol Biomarkers Prev. 2005; **14(8):** 1847-50.

[xv] 8. Prevention CfDCa. Fourth national report on human exposure to environmental chemicals, Updated tables. Atlanta, GA: Centers for Disease Control and Prevention; 2012 February, 2012.

[xvi] Needham LL, Grandjean P, Heinzow B, Jorgensen PJ, Nielsen F, Patterson DG, Jr., et al. Partition of environmental chemicals between maternal and fetal blood and tissues. Environmental science & technology. 2011; **45(3):** 1121-6.

[xvii] Landrigan PJ, Schechter CB, Lipton JM, Fahs MC, Schwartz J. Environmental pollutants and disease in American children: estimates of morbidity, mortality, and costs for lead poisoning, asthma, cancer, and developmental disabilities. Environmental health perspectives. 2002; **110(7):** 721-8.

[xviii] Grandjean P, Bailar JC, Gee D, Needleman HL, Ozonoff DM, Richter E, et al. Implications of the Precautionary Principle in research and policy-making. American journal of industrial medicine. 2004; **45(4):** 382-5.

[xix] Grandjean P, Eriksen ML, Ellegaard O, Wallin JA. The Matthew effect in environmental science publication: A bibliometric analysis of chemical substances in journal articles. Environ Health. 2011; **10(96):** 96.

[xx] Diamanti-Kandarakis E et al. *Endocrine-Disrupting chemicals: An Endocrine Society Scientific Statement*. Endocrine Reviews. 2009; 30(4):293-342. http://www.endo-society.org/journals/scientificstatements/upload/edc_scientific_statement.pdf

[xxi] Gee D. *Late lessons from early warnings: Toward realism and precaution with endocrine-disrupting substances*. Environmental health perspectives. 2006; 114 Suppl 1: 152-60