PROGRAM

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NEUREOH 2008 June 11-13

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Multiple Exposures, Multiple Effects

Heredia, Costa Rica

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Roberto Lucchini is an occupational health professional and holds a Professorship in Occupational Health at the Medical School and the Residency School in Occupational Health of the University of Brescia, Italy. Dr. Lucchini obtained his medical degree from the University of Brescia in 1987, and completed a residency in occupational health at the University of Parma, Italy, in 1991. He followed the Intensive Residency in Occupational Health at the Extended Program in Medical Education of the University of California, San Francisco, USA, in 1988, and various international courses in Neurotoxicology in Sweden and Finland. From 2004, he is an Associate Researcher at the University of California Santa Cruz, Department of Environmental Toxicology Program and from July 2006 he holds a Visiting Professorship at the Harvard School of Public Health, Department of Environmental Health.

His main research areas include:
A)Early neurotoxic and neurobehavioral effects due to occupational and environmental exposure to neurotoxic agents such as manganese, mercury, lead and solvents;
B)Neurodegenerative disorders (Parkinson's disease and Alzheimer disease) in relation to occupational and environmental exposure to neurotoxic agents.
He has published over 100 peer-reviewed papers on various subjects related to Occupational Health and Prevention. Since 1994 he has served as member of the ICOH (International Commission on Occupational Health) Scientific Committee on "Neurotoxicology and Psychophysiology. He was appointed Secretary elected of this Committee from 1999 to 2005 and as Chairman elected for the triennium 2006-2009. He is an international contributing editor of the 'American Journal of Industrial Medicine', and member of the Editorial Boards of 'Neurotoxicology', 'Science of Total Environment', and 'Industrial Health'.

Roberto Lucchini es un profesional en salud ocupacional y actualmente se desempeña como profesor de dicha área en la Escuela de Medicina y en la Escuela de Residentes en Salud Ocupacional de la Universidad de Brescia en Italia. Obtuvo su título de médico en la Universidad de Brescia en 1987, y completó una residencia en salud ocupacional en la Universidad de Parma, Italia en 1991. Siguió la Residencia Intensiva en Salud Ocupacional en el Programa de Extensión de Educación Médica de la Universidad de California, San Francisco, Estados Unidos, durante 1988, así como varios cursos internacionales en neurotoxicología en Suecia y Finlandia. Desde el 2004, es investigador asociado al Departamento de Toxicología Ambiental de la Universidad de Santa Cruz en California, y desde julio del 2006 es profesor visitante del Departamento de Salud Ambiental de la Escuela de Salud Pública de Harvard.

Sus principales áreas de investigación son:
A)Efectos neurotóxicos y neuroconductuales debido a la exposición ocupacional y ambiental a agentes neurotóxicos como el manganeso, mercurio, plomo y solventes.
B)Desórdenes neurodegenerativos (enfermedad de Parkinson y enfermedad de Alzheimer) en relación con la exposición ocupacional y ambiental a agentes neurotóxicos.
El Dr. Lucchini ha publicado más de 100 artículos con revisión de pares sobre diferentes

temas relacionados con la Salud Ocupacional y la Prevención. Desde 1994 es miembro del Comité Científico de Neurotoxicología y Psicofisiología de la Comisión Internacional en Salud Ocupacional (ICOH por sus siglas en inglés). Fue Secretario electo de este comité entre 1999 al 2005 y es Presidente electo del mismo para el triennium 2006-2009. Él es un editor internacional del "American Journal of Industrial Medicine" y miembro del Consejo Editorial de "Neurotoxicology", "Science of Total Environment" e "Industrial Health".

Lifetime neurotoxic exposures as a potential threat for neurogeneration: Need for prevention strategies on a global scale

Roberto Lucchini

Exposure to neurotoxic agents is becoming more and more a common event in the workplace and in the general environment. This is mainly due to the fact that the already large number of neurotoxic substances is constantly increasing with newly generated compounds that are needed for a rapidly changing market. Considering the recent history of neurotoxicology, it is also quite evident that the exposure scenarios are rapidly evolving in terms of intensity, but also regarding spatial and temporal dimensions, leading towards the condition of "lifetime" exposure in the population. This can be particularly dangerous, especially when dealing with substances that besides acute toxicity, are able to accumulate in the body and cause long-term cumulative effects. Exposure intensity has been markedly decreased in the workplaces, much more evidently in the developed world, but with positive signs of improvement also in the developing countries, where raising awareness programs like the one on mercury toxicity by the United Nations Environmental Program (UNEP) have favored the adoption of preventive actions. If this improvement is well documented for traditionally known agents like lead, mercury, manganese, aluminum, toluene, xylene, styrene, acrylamide, ethylene oxide, and others, new substances and compounds are being constantly introduced, and the toxicological knowledge is always very limited. At the same time, exposure is no longer confined in the workplaces but is rapidly expanding to the general environment in many ways. Due to the active transportation of ultra fine particles by winds, direct emissions in the air, water and soil, can increase exposure levels also at a considerable distance from the point sources, as shown by the presence of various contaminants in the Artic that have been originated by industrial and agricultural activities (Macdonald et al., 2000). Contamination of soil and water from industrial emissions and wastes and from pesticide application favors the entrance of neurotoxicants in the food chain through the crop, fish and drinking water. Therefore dietary exposure adds on dramatically as an indirect carrier able to reach every human being on the planet regardless the distance from the contamination and exposure sources.

Finally, the temporal dimension is gaining more and more importance in the neurotoxicological context due to the combination of different aspects: a) the constant increase of average life expectancy and working life, and b) the presence of pre- and postnatal exposure. The combination of these conditions is also of particular concern, because in addition to increasing the total duration of exposure through the lifetime, it introduces the importance of "when" exposure takes place in life, which can be a critical parameter besides the quantitative ones. From the very beginning of the embryonic development through infancy, puberty, adulthood, and old age, the human body faces critical stages. The same exposure dose can cause different neurotoxic effects according to relative conditions of hypersensitivity (figure 1). Pre- and post-natal exposure is particularly dangerous in this context, due to the high vulnerability of the developing brain to neurotoxicants whose hazardous properties are largely unknown and underestimated.

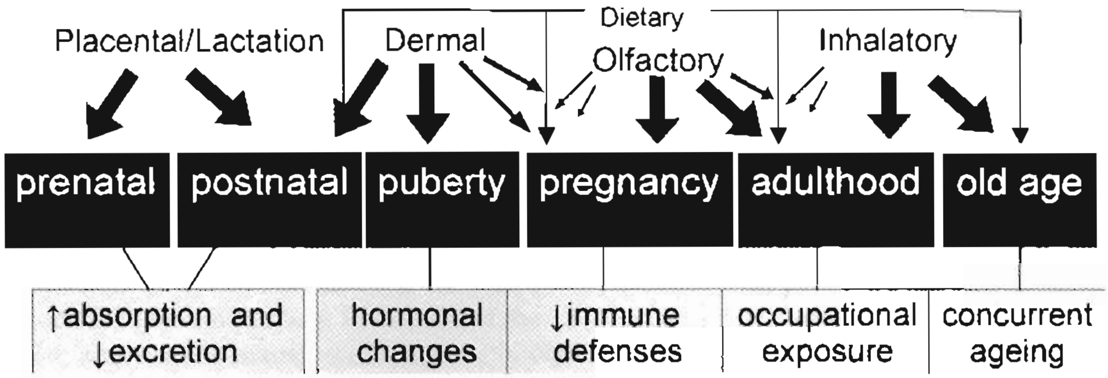

Figure 1: Exposure to neurotoxicants through lifetime with the different exposure routes in the first row, the different stages in development in the second row, and the critical conditions in the third row.

The considerations from above imply that the concept of exposure is changing very rapidly. Almost unique consideration has been given to exposure intensity as expressed by the dose concept, starting in the Middle Age with Paracelsus and continuing today with modern occupational and environmental toxicology that have developed a consolidated knowledge in environmental measures and biological monitoring as suitable basis for exposure assessment. Safe exposure levels have been identified in risk assessment as mainly based on current exposure dose and intensity.

The changes in exposure scenarios, the importance of cumulative rather then acute or subacute manifestiations of neurotoxicity, require now a substantial modification to this approach. In fact, according to the Heber's Law, exposure is the product of intensity and duration and the final product does not change when intensity decreases and duration increases. Therefore, the final outcomes of health effects may remain as an uncotrolled risk factor if preventive measures are not undertaken correctly. A non adequately controlled exposure to various neurotoxicants, starting during fetal life and continuing through infancy, puberty, adult life with eventual occupational exposure, may likely pose a high risk for long-term neurodegenrative effects in the population.

Regulatory agencies are not addressing the issues in a proper way, because the procedure for the definition of preventive policies is often too slow, in some cases inadequate, and rarely aimed to protect from lifetime exposure. Regulatory bodies should proceed with a more timely-oriented agenda in the definition of protective sandards for the newly produced compounds and also with a more frequent re-evaluation of already defined safe exposure levels. This is made possible today thanks to a costantly increasing scientific production in the area of neurotoxicology, and to the availability of reliable methods for the assessment of the Nervous System. The REACH program in the EU offers good chances for prevention, by controlling the immission of newly produced substances with potential neurotoxicant properties, and imposing the registration and evaluation with toxicity testing, in order to authorize industrial and commercial use. Unfortunately, testing for neurodevelopmental toxicity is not required by this regulation. Data on the developmental effects due to peri-natal exposure, are lacking for the majority of neurotoxic substances, therefore the use of uncertainty factors is necessary to protect theindividuals from this type of exposure. This procedure of conventional risk assessment is highly imprecise and should be avoided by increasing t he availability of scientific information, and this can be obtained only by increasing resources for research in neuro-developmental toxicology.

An example of a neurotoxicant with known cumulative mechanism of toxicity is manganese (Mn), that tends to accumulates in the brain because of a very slow elimination rate. In case of exposure to levels exceeding the homeostatic range of this essential element, an overload condition can be established with possible late effects consisting in increased risk of Parkinsonism. This has been shown in welders and in populations with prolonged environmental exposure to industrial emissions and car traffic with the use of Mn-based additive in gasoline. At this regard, concern is raised also for populations with high Mn content in drinking water, like in Bangladesh. Exposure to Mn can start during the pre-natal life through the mother's exposure and consequent passage through the placenta. Absorption of highconcentrations, exceeding homeostatic range, can take place also post-natally. Being an essential element, Mn is needed by the organism and especially for the developing brain, as a constituent of important metalloenzymes such as arginase, glutamine synthetase, pyruvate carboxylase and superoxido-desmutase. In order to provide Mn to the developing brain, the intestinal absorption of this element is high, whereas the excretion rate is low, due to the incomplete development of the biliaric pathway, mostly responsible for Mn elimination. High concentration of Mn in maternal milk and formulas can further increase Mn overload. This may further continue during childhood and adulthood for environmental and/or occupational exposure. The main target of toxicity are represented by coordination of fine movements, cognitive functions related to memory, and aggressive behavior. The need to protect from health effects due to a life-time exposure to these neurotoxicants, requires that in the assessment of dose-effect-response, adequate exposure metrics are used, able to reflect the body burden and represent cumulative exposure. These metrics should be ideally obtained with suitable biomarkers, or with cumulative exposure indices that approximate long-term exposure.

Health Canada, the Canadian federal department of health, has conducted a new human health risk assessment for inhaled Mn (http://www.hc-sc.gc.ca/ewh-semt/air/out-ext/_consult/index_e.html). The derivation of the air quality guideline was based on an occupational dataset with available information on the average respirable exposure over the lifetime of the subject and average respirable exposure over the 5 years prior to testing. The indices had been calculated by multiplying the available annual average concentration for each worker for the number of exposure years. A range of guidance values derived was derived based on the cumulative exposure metrics. Uncertainty factors had to be introduced to reduce the imprecision related to several issues, such as the use of data from an occupational population, the protection of more sensitive subgroups of the population, the relative imprecision of the cumulative exposure indices to cover the entire lifetime: nevertheless, this procedure is an example of how protective exposure levels should take into account exposure metrics aimed to cover the lifetime exposure.

The current estimates predict an astonishing tendency to an increase of neurodegenerative diseases in the next years, and this not only for older individuals. Therefore, the trend may not only relate to the increasingly aged population per se, but also to the exposure to neurotoxicants. Parkinson Disease is estimated to increase substantially and mostly in those countries with poorly controled exposure conditions, like China, India, Brazil, and Bangla Desh. An important part of these diseases may likely be the results of non adequate control of lifetime exposure to neurotoxicants. Therefore, there is a clear need to adopt more precise preventive actions that are beased on information regarding cumulative and lifetime exposure. These policies shouls be adopted not only by the indutrialized countries but also in the developing areas of the world, where high exposure levels to neurotoxicants are likely to increase the risk for neurodegenerative disease in the next future.