EVALUATION OF THE LINK BETWEEN CHEMICAL ENVIRONMENT, OBESITY AND DIABETES

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SUMMARY

Metabolic diseases: a worldwide epidemic

In 2008, non-communicable diseases – or NCDs – accounted for 36 million deaths worldwide, the equivalent of 60% of deaths [versus 40% for nosogenic diseases]; of these, 80% were [observed] in low-income or middle-income countries. According to *WHO*, the ratio is expected to be 70%/ 30% by 2015. The situation triggered the opportunity for *WHO* to convene a high-level meeting within the United Nations General Assembly to take action against what is considered as a worldwide epidemic. The Member States adopted 'an action-oriented outcome document' to enforce prevention and treatment policies for such diseases and they acknowledged that '*those diseases represent a major challenge to sustainable development in the 21st century'.*

In a conference draft document, Margaret Chan, Director-General of the *World Health Organization*, stated that '*for some countries, it is no exaggeration to describe the situation as an impending disaster for health, for society and most of all for national economies […] that could reach levels beyond the coping capacity of even the wealthiest countries in the world, if the unhealthy lifestyles that are at the root of the epidemic are not actually addressed*.'

Metabolic diseases rank first. According to *WHO,* it is estimated that, by 2015, 700 million people will be obese, which accounts for a 75% increase over 10 years. Diabetes is one of the major consequences of obesity, although it also has specific causes. In 1995, it affected 30 million persons worldwide. It currently affects almost 220 million(s) and it is expected to concern 366 million(s) by 2030. According to the French 2009 *ObEpi* study, 32% of those above 18, *i.e.* 14 million individuals, are overweight and 14.5%, *i.e.* 6.5 million(s), are considered as obese. The proportion doubled between 1997 and 2009.

According to the long-term disorder [ALDs] figures issued in France by the Public Health Insurance System [PHIS], diabetes incidence almost doubled between 2000 and 2008 [+ 93%] and prevalence was estimated at around 1.8 million(s) with 90% being type 2 diabetes cases directly linked with obesity. In France, diabetes has an annual additional cost of 1 billion €. Even though both epidemics might be correlated, they should be considered separately, since every obese person will not become diabetic [ca. 25%], while more than 60% diabetics are obese.

Find the complete file "*Chemical environment, obesity and diabetes*" online (in French only) : http://reseau-environnement-sante.fr/wp-content/uploads/2012/03/Rapport_ECOD_VF.pdf

Metabolic syndrome [Syndrome X] is characterized by a combination of medical disorders having a carbohydrate and lipid origin such as hypertriglyceridemia and hypercholesterolemia associated to fatty overweight, pro-inflammatory state, hypertension, which pave the way to Type 2 diabetes and cardiovascular diseases.

Syndrome X is not considered as pathology *per se*, yet it involves a set of metabolic and functional anomalies that are forerunners to the pathology. In France, prevalence was estimated in 2004 between 16% and 22.5% [among men] and between 11% and 18,5% [among women], depending on definitions and studies.

Chemical pollution: a third factor to account for metabolic diseases.

Since the 80s, the importance of hygiene and diet measures has been systematically emphasized as a means to lower the impact of obesity and diabetes. This strategy would heavily rely upon the assumption that obesity was the consequence of the discrepancy between an increasingly overenergetic food *vs.* a more and more limited physical activity. The process would worsen for certain individuals because of genetic polymorphisms of susceptibility. Various action-oriented programmes based on this analysis have been set up, yet one has to admit that no significant result was achieved and the epidemic could not be stopped.

In recent decades, increasing scientific data simultaneously highlighted the significant role played by chemical pollution in the epidemic, more specifically chemical pollution by EDCs [Endocrine Disrupting Chemicals].

The term *endocrine disruptor* was coined 20 years ago at the *Wingspread Conference*, that was followed by the *Wingspread Consensus Statement* by the participants to the workshop gathered around Theo Colborn whose book, *Our Stolen Future*, provides the foundation of the concept. Initial emphasis was put on the impact of EDCs on reproduction, but it was discovered during the past decade that the health impact actually went far beyond the sole effects on reproduction.

It currently is a well-acknowledged fact that viewing adipose tissue only as a passive reservoir for energy storage is no longer valid, and that it should definitely be considered as a hormone-induced organ, much similar to an endocrine gland on account of the numerous chemical transmitters that it releases. As such, it might be disrupted by obesogenic and diabetogenic [obesity-inducing & diabetes-inducing] substances which started being widely used after WW2 and have contaminated humans and ecosystems.

These substances mainly are organochlorinated substances called Persistent Organic Pollutants [POPs] on account of their high stability. They have been developed as pesticides, e.g. DDT, or as fireproof agents, e.g. PCBs [Polychlorinated biphenols]. Although their use has been banned, these substances and their by-products such as dioxins persist in the environment. Alternative products

like polybrominated chemicals [biphenols] were found to have the same properties and yet only some of them have been withdrawn from the market so far. Perfluorinated chemicals are currently a point of focus, as some studies have shown a link with hyperuricemia, a bioindicator whose increase is a marker of diabetes onset.

Other endocrine disruptors, e.g. BPA [Bisphenol A] and phthalates, are notably present in homes *via* plastic materials, and via foodstuffs, because of contamination by food containers. Pesticides like organophosphate compounds and atrazine are endocrine disruptors too. Contamination of human populations by these substances is almost general in all countries.

Endocrine Disruptors: A Change of Paradigm

It is now a well-established fact that endocrine disruptors do not match the conventional classical toxicology principle that provides the basis of current regulations for chemical substances, as summarized in Paracelsus' paradigm 'The dose makes the poison.'

In 2009, in order to account for the action of endocrine disruptors, the US *Endocrine Society* issued a new paradigm that is based on the statement: 'The period makes the poison'. Toxic effects are mainly those that will appear during childhood and adulthood, and even across the following generations, as a consequence of exposure during pregnancy. The dose-effect relationship is not linear: it is generally observed that a weaker dose will trigger a stronger effect; the effect might be amplified whenever co-exposure occurs [*cocktail effect*], which reflects the reality of human exposure(s). The transgenerational transmission is achieved through epigenetic pathways providing the foundations for 'the developmental toxic origins of pathologies among teenagers and adults' that many among the scientific community currently put forward.

Distilbene [DES] was used as a synthetic hormone drug in the post-war period until the early 1970s; it clearly displayed evidence that the impacts experimentally observed for endocrine disruptors would apply in humans.

This change of paradigm was adopted by *ANSES* in its latest report on BPA and very recently by the *Académie de Médecine* in its report on cancer & endocrine disruptors.

Obesity- & Diabetes-inducing substances: experimental & epidemiological evidence

Une étude réalisée par la biologiste du NIEHS Suzanne Fenton montre que des souris exposées pendant la période prénatale au PFOA étaient plus susceptibles de devenir obèses à l'âge adulte.

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More and more experimental data show disruption of carbohydrate and lipid metabolism by such endocrine disruptors, more specifically at impregnation levels that concern human populations. Low doses of BPA, phthalates and organotin compounds induce obesity among animals if exposed in utero or during lactation. Moreover, insulin resistance increases whenever low dose exposure to these substances occurs.

A wide range of in vitro and in vivo studies suggest that POPs are stored in adipose tissue and can therefore impact insulin secretion and interfere with adipogenesis. Heavy metals like cadmium, mercury and/or arsenic as well as fine particles [PM 2.5 → Particulate Matter, 2.5 micrometers or less] will disrupt insulin metabolism mainly via the oxidative stress mechanism. We now speak of obesogens (obesity-inducing) and diabetogens (diabetes-inducing) pollutants to characterize the adverse pathophysiological effects triggered by those substances.

Epidemiological surveys conducted as part of large programmes like the *National Health and Nutrition Examination Survey* [*NHANES*] cohort in the US, have highlighted excess diabetes in the overall population impregnation by POPs, cadmium or atmospheric exposure to fine particles [PM 2.5], adjusted for body mass index [BMI]. In the countries that have been more significantly affected by arsenic water pollution, there is a well-established link between water pollution and diabetes. Excess diabetes has been found too in populations classified as occupationally exposed to certain organochlorine and organophosphate/ organophosphorus pesticides. The extent to which these survey findings can be generalized to the overall population remains uncertain for those pesticides.

Co-exposure of excessive caloric intake and diet combined with chemical pollutants may potentiate obesity or diabetes [BPA, atrazin, POPs, arsenic].

Other compounds like sweeteners that do not act via the endocrine disruptor mechanism may indirectly also induce obesity and diabetes. Prenatal exposure to maternal smoking induces obesity and diabetes – it could be in fact acting as a co-factor.

Further research obviously needs to be developed in this area. Yet, sufficient data are available to address chemical pollution as an additional research strand besides the traditionally considered food and inactivity factors so as to better understand the obesity & diabetes epidemic. This topic should be a subject of mutual

consideration in the national implementation plans *PNSE* [French National Health and Environment Plan], *PNNS* [French National Health & Nutrition Plan] and *Plan Obésité* [French Action Plan on Obesity], that have not taken it into account so far.

A significant research effort should be undertaken to identify new pollutants. The priority should be to specifically scrutinize the impact of currently listed endocrine disruptors on carbohydrate and lipid metabolism. Such an effort should more specifically focus on identifying the cross-generation effects linked to co-exposure by three factors, e. g., food, inactivity and chemical pollutants.

The issue of protecting people affected by obesity and diabetes from further exposure to obesogenic and diabetogenic substances should be also considered by the French HAS (Upper Health Authority) in complement to diet and lifestyle recommendations.

On a wider scale, the obesity and diabetes challenge strengthens the need to tackle the issue of endocrine disrupting chemicals as a whole. This direction is put forth by US Senator John Kerry in his *Endocrine Disruption Prevention Act*, a bill presented in the US Senate on December 3, 2009: '*parents' bodies must be free of EDC's prior to conception, during gestation, and throughout lactation*.'

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