Health Issues of 21st Century Food Packaging

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In the last few years, the issue of Sustainable Development has gained importance in the food packaging sector. Environmentally friendly packaging often is also called "sustainable", and it is mainly associated with reduced CO_2 emissions during production and transport. With the current debate on climate change, these are important issues and in terms of environmental protection their gaining importance in the business world certainly is laudable. However, the concept of Sustainable Development goes beyond energy use and contribution to climate change. The concept of Sustainable Development as described in "Our Common Future" (1987) is about developing our society, preserving the natural environment for next generations, and using resources in a non-exploitive, sustainable way. Important about this idea is that it must be specifically defined for every context it is applied to.

Table 1: Ideal food packaging fulfills high demands.

- protects food from outside influences
- protects food from damage
- provides information to consumers
- is convenient
- permitts product traceability
- allows product marketing
- is tamper-proof
- does not affect the food‘s quality
- is healthy
- can be produced with minimal environmental impact (chemical pollution, energy, emissions)
- ...?

For understanding Sustainable Development in the area of food packaging, the main functions of food packaging first need to be characterized (Table 1). Criteria are defined for the economic, social and environmental dimensions of Sustainable Development (Figure 1; non-extensive criteria listing). One major aspect certainly is health: Food packaging that has negative effects on human health is not aligned with Sustainable Development. Therefore, concentrating exclusively on carbon footprint and/or energy consumption will not guarantee a packaging solution that can be considered overall "sustainable".

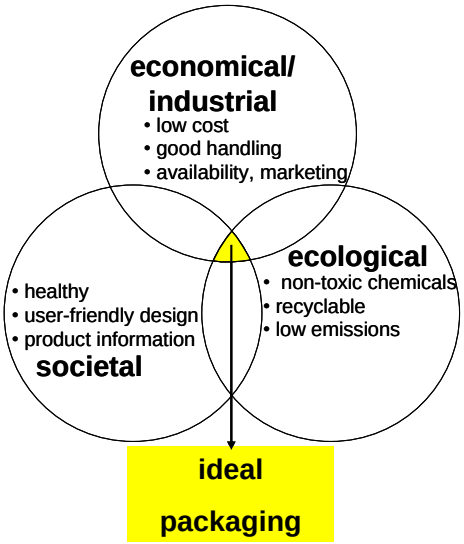

Figure 1: Some selected aspects of ideal food packaging, in the context of Sustainable Development.

The focus of this article is on food packaging, where the food contact material is plastic because this type of packaging is by far the most abundant. Around 70% of all consumer packaging is for food and beverage (World Packaging Organization and Pira International 2008); when broken down by packaging material, the most important consumer packaging (by market value) is made of plastic (38%, both rigid and flexible plastics), followed by paper and cardboard (30%), metal (19%), glass (8%), and others (5%) (Pira International, in:(Rexam 2008)). Metal, paper and cardboard food packaging mostly is coated with an internal plastic food contact material, essentially making plastics the main food contact material (Castle 2007).

Plastics are made from side products of oil refinery. The basic building block of any plastic is the monomer, a molecule which is linked in a chain to other identical monomers, forming the polymer. Polymers are made up of ten thousands of monomers, and the polymerization reaction is a complex chemical process for which other chemicals (like catalysts) are required. Additives are added to the polymer to enhance the plastic material properties, like softeners or UV absorbers (Piringer and Baner 2000). The final plastic material thus is a mix of polymer, additives, manufacturing aids, and side-products from the complex polymerization process that were not intentionally added (NIAS: non-intentionally added substances) (Bradley and Coulier 2007).

Additives, NIAS and unreacted monomers are not chemically bound to the polymer. They can get out of the plastic material by diffusion. If the plastic is used as a food contact material the food can be contaminated by these chemicals, a process known as migration. Migration depends on the plastic material and the chemistry of the packaged foodstuff, it also is affected by the thickness of the packaging material and the size of the packaging (surface to volume ratio), it is enhanced by heat, and increases with storage

time (de Fatima Pocas and Hogg 2007). When purchasing plastic packaged food consumer have no information on how the food was stored (temperature, sunlight) or for how long—aspects that will influence the degree of packaging compound migration into food.

Not all compounds that can migrate from plastic packaging are identified, because plastic is chemically very complex. When extracts from plastic materials are analyzed for their components chemists speak of the "Forest of Peaks" because the measurement plots have many different peaks (Figure 2). Each peak—or "tree"—in this forest is a different chemical substance. Thus it is clear that "plastic" is not one homogeneous material but a complex mixture of many different chemicals that are present at different concentrations.

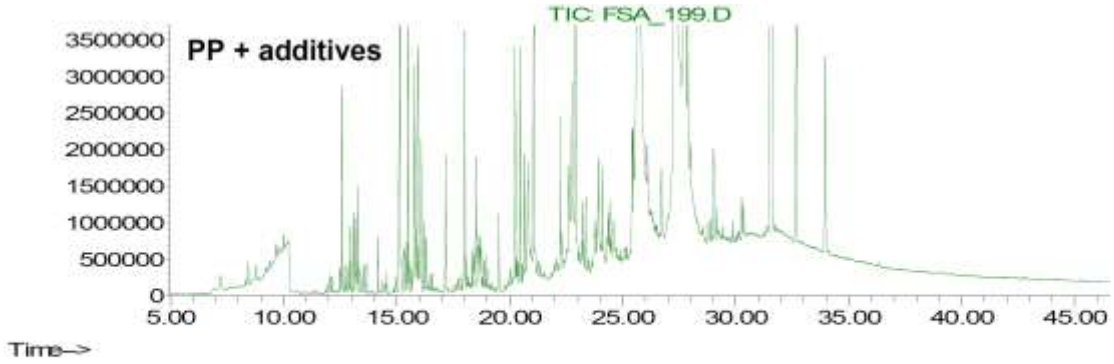

Figure 2: A plastic organic extract (Polypropylene+additives, extracted with ethanol) analyzed using gas chromatography-mass spectrometry (GC-MS). Each peak represents a different chemical (reproduced from (Bradley and Coulier 2007)).

For regulatory purposes, only the most abundant compounds are looked at, and toxicological risk assessment is carried out for the single substances, not for the finished material. This means that compounds which are present at levels below a defined threshold are not characterized for their toxicological properties. In addition, substances that are unknown (i.e. unidentified) are not quantifiable. Therefore verification if these compounds in fact are below the threshold is not possible. As a consequence, certain compounds present in plastic food contact material potentially could migrate into food, but the chronic exposure to such substances is not assessed. The long-term safety of plastic food contact material essentially remains unknown (Muncke 2009).

The concept of thresholds for toxicological risk assessment is based on the old paradigm of toxicology by Paracelsus. He was the first to relate the dose of a chemical to the toxic effect and stated that "only the dose makes the poison". Basically, this paradigm means that each chemical has a "toxic level" and a "non-toxic" level at which exposure will not result in adverse health effects. Hence, chemicals present in food, even if they are unknown, will not be a health hazard as long as they are below a certain concentration. This paradigm of toxicology is the basis of current chemical risk management (further information: (van Leeuwen and Vermeire 2007)).

Paracelsus lived in the 16th century. During the last 20 years toxicological sciences have changed substantially; new methodologies have been developed, leading to new paradigms. Today we know that "the dose makes the poison" must be complemented by other aspects, for instance the timing of an exposure. Developing life is far more susceptible to chemicals during certain stages, and the placenta does not form a perfect barrier for all chemicals (Bern 1992). Compounds that can mimic hormones are another concern, because they can be potent at low doses, while at higher concentrations they will exert other effects (Weltje et al. 2005). Such substances are called *endocrine disrupters*, or environmental hormones.

Environmental Hormones (Endocrine Disrupters)

Our bodies are controlled by hormones, molecular signals that enable communication between cells, tissues and organs. They also control organ formation in the developing fetus. Many different types of hormones exist, but the best known are the sex hormones estradiol and testosterone. Estradiol is associated with "female" and testosterone with "male", but both men and women have both hormones, the difference being the concentration. In women, estrogen levels generally are much higher, while men have more testosterone.

Environmental hormones (endocrine disrupters) are compounds that mimic the biological action of endogenous hormones, or in general disrupt the hormone system. These can be natural compounds found in plants, or industrial chemicals with a wide array of uses. Both types are found in the environment, hence the name. In particular the group of "xeno" (Greek for foreign) estrogens comprises many different chemicals and their effect is often described as "estrogenicity". They all have a partial estrogen-mimicking property and are the best studied type of endocrine disrupter (Safe et al. 2001).

Human exposure to xenoestrogens is a health concern, because these substances can disrupt the natural hormone estrogen and lead to adverse health effects. This is known from one tragic example, where a xenoestrogen was given as anti-abortive pharmaceutical to around 8 million of pregnant women worldwide from the 1940s to 1970s. This compound, called DES (for diethylstilbestrol), crossed the placenta and affected development of the fetus. One outcome of this medical intervention was the increased occurrence of a rare cancer in young women which eventually let to the termination of DES prescription. Another observed effect is an increased risk for breast cancer in women older than 40 that had been exposed as fetus' to this chemical. Possibly even the grandchildren of DES-taking mothers will have increased risks for cancers, as this has been shown to be the case in animal experiments (Newbold et al. 2006).

Low doses - significant effects

One property of environmental hormones is their non-monotonic dose-response curve. This means that in the low-dose range such compounds have an effect, but when the concentration is increased this effect decreases, and another type of effect can occur, or possibly even the opposite effect is seen (an example is Tamoxifen, a breast cancer medication that will stimulate tumor cell growth at low doses and inhibit it at higher concentrations). This is in direct contradiction to Paracelsus' paradigm which proclaims that increasing concentrations will lead to increasing effects (Myers et al. *in press*?).

The most extensively studied xenoestrogen is bisphenol A. Also known as BPA, it is used in food packaging and can leach from the packaging into food. The estrogenic properties of BPA have been known since the 1930s, when its pharmacological use was investigated. Since the 1950s BPA is used as a monomer for polycarbonate plastics and epoxy resins that line food and beverage cans. In the last few years the discussion about the safety of BPA has intensified, especially because of BPA-leaching polycarbonate baby bottles that expose infants to low-doses of this substance. Canada is the first country to ban bisphenol A-based baby products. The main use of BPA today is for CDs and DVDs, and it is a high production volume chemical with estimated >4Mio t global annual production in 2006 (Senjen and Azoulay 2008).

Because of its extensive use, human exposure to BPA is ubiquitous, but its long-term health effects are not known. An ongoing national study in the US, the National Health and Nutrition Examination Study (NHANES) has a large database of health and body burden data that monitors the US population. Recently, a study using this data was published in the Journal of the American Medical Association (Lang, Galloway et al. 2008). In the NHANES study, participants are asked if they suffer from certain medical conditions. Lang and coworkers, authors of this recent study, statistically correlated this yes/no information with levels of BPA measured in the participant's urine, which is a good measure of a person's BPA body burden (Figure 3).

Their findings were surprising: participants that suffered from cardiovascular/heart diseases had significantly higher BPA body burdens than healthy participants. The same correlation was found for diabetes patients, who also had significantly higher BPA levels. For other diseases like cancer no association was found with BPA levels.

These results are highly relevant because they are the first epidemiological study for BPA, in a large population sample. It is important to note that they do not show causation. However, exposure to BPA is prevalent in the US population, with 93% having detectable levels. At the same time, 8% or more of the US inhabitants suffer from diabetes. This study indicates a potential link between the high exposure and incidence of disease, and asks for further understanding of possible causes.

It is interesting to note that both diabetes and cardiovascular disease develop from the same sub-clinical condition known as *metabolic syndrome* or *insulin resistance syndrome*

(Figure 4). Insulin is the body's hormone that regulates blood sugar levels and is central in controlling energy metabolism. If the body fails to control insulin levels, insulin resistance can develop.

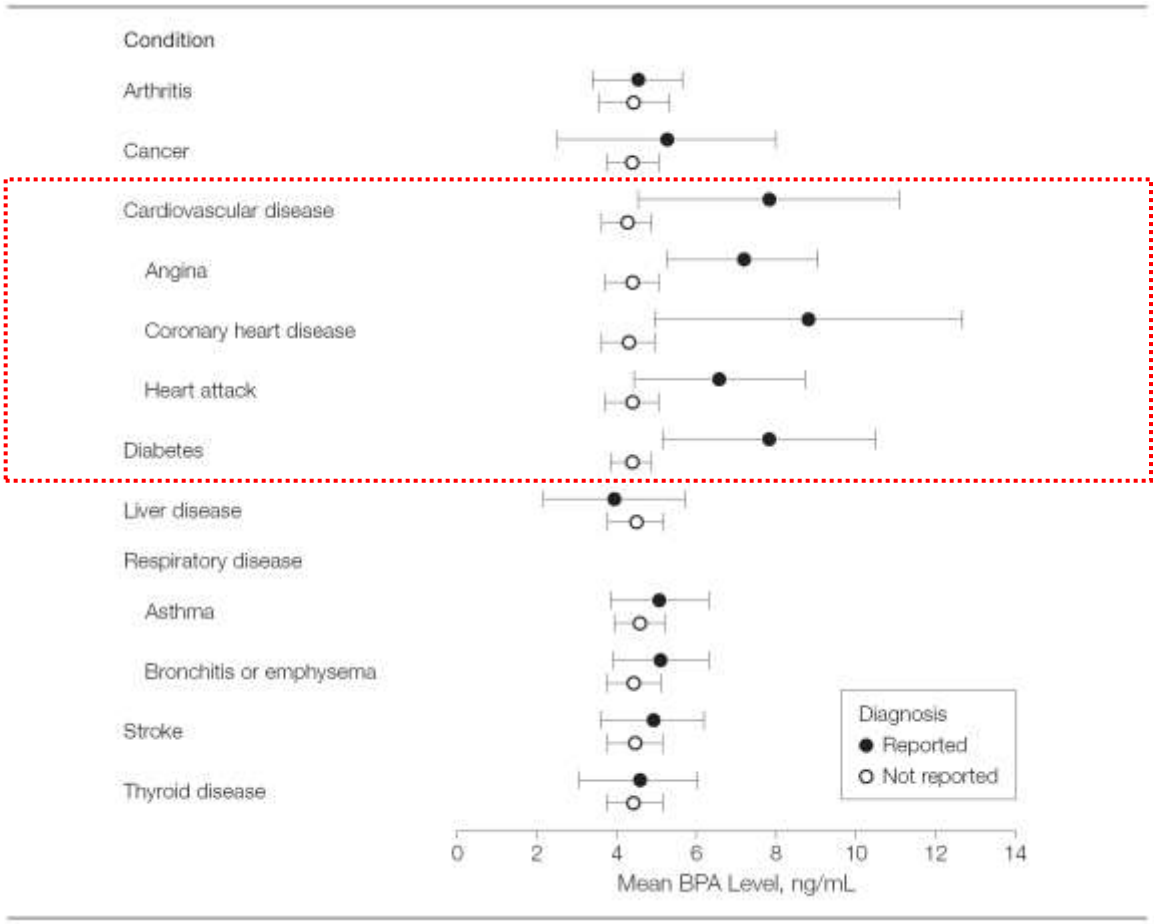

Figure 3: Estimated average BPA concentrations in relation to reported diseases and conditions. Estimates adjusted for age and sex. Error bars indicate 95% confidence intervals. (reproduced from (Lang, Galloway et al. 2008)).

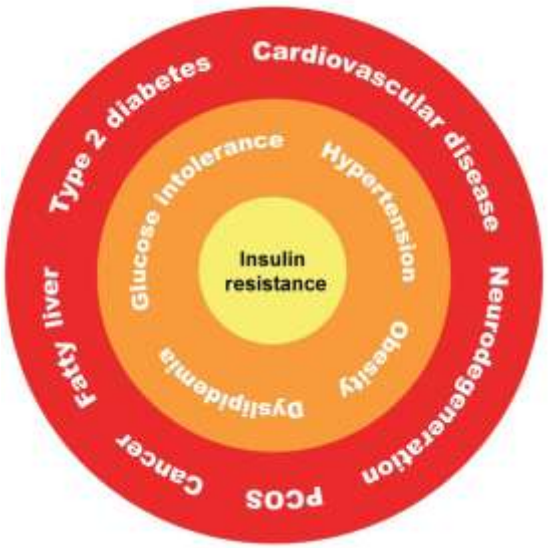

Figure 4: Insulin resistance, the failure of insulin target cells to respond to blood insulin stimulus, can develop into a number of diseases (red circle). The orange circle shows symptoms of the metabolic syndrome. (reproduced from (Biddinger and Kahn 2006))

In animal experiments it has been shown that BPA indeed can lead to insulin resistance (Alonso-Magdalena, Morimoto et al. 2006). Male adult mice received either a single dose of BPA at one fifths of the current FDA's Tolerable Daily Intake (TDI) level, or a single dose of estradiol at the same concentration as BPA. The animal's blood insulin level was then measured, and both estrogen and BPA treated animals showed a marked and statistically significant increase compared to the untreated control animals ("Vehicle") (Figure 5). When these animals were treated for 4 subsequent days they became insulin resistant.

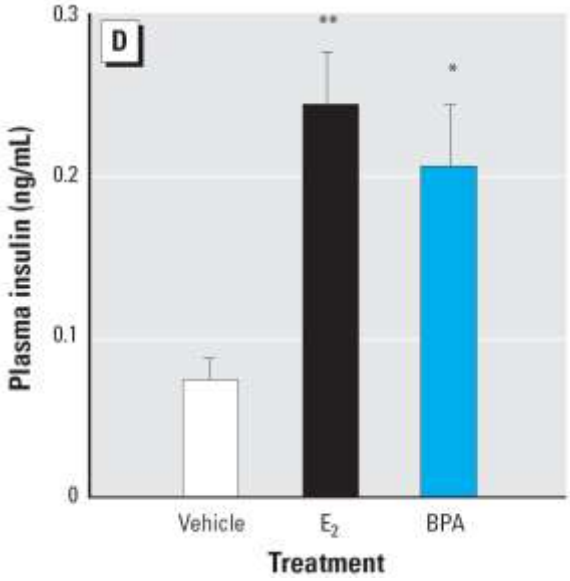

Figure 5: Male adult mice were treated with a single dose of either BPA or estradiol (E2). Compared to the controls ("Vehicle") both treatments significantly increased blood (=plasma) insulin levels. If repeated on 4 subsequent days the animals became resistant to insulin. (reproduced from (Alonso-Magdalena et al. 2006))

From these experiments it is clear that BPA is not a weak xenoestrogen; it is able to induce some of the same effects like the natural hormone estradiol, at the same concentration levels. This finding is of serious concern for public health.

BPA Affects Obesity-Protective Hormones

Currently, around 60 Mio US inhabitants are obese, meaning that they have a body mass index (BMI) that is larger than 30. About one third of the US population, or 100 Million, are overweight (BMI>25). Obesity is currently one of the most pressing needs in terms of public health prevention and management.

The causes for obesity are manifold. In addition to nutrition and lack of exercise, chemical pollutants are being discussed as possible cause of obesity. BPA is one of the compounds that has been named an "obesogen".

In this context, another recent study looked at BPA's role in adiponectin release. Adiponectin is an endogenous hormone that is negatively correlated with insulin and body fat levels in adults. It is a counter balancing factor to insulin. In this study, human fatty tissue was taken from abdominal reduction surgery (e.g. "tummy tuck") and grown as cell culture. The cells were treated either with BPA or estradiol, at different concentrations, and the release of adiponectin from the treated cells was assessed (Figure 6).

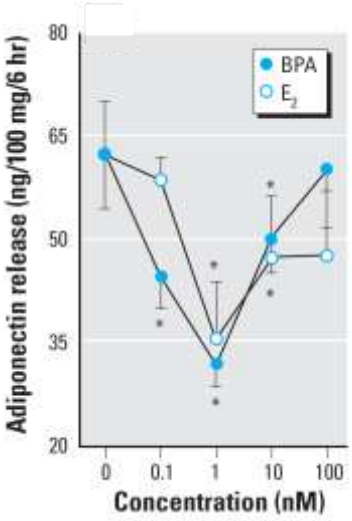

Figure 6: Release of the hormone adiponectin from human fatty tissue in response to treatment with BPA or estradiol (E2). Both low doses of BPA and E2 reduce adiponectin release in a statistically significant way (marked with *), while higher doses of BPA do not. (reproduced from (Hugo et al. 2008))

Both low doses of BPA and E2 statistically significantly reduced adiponectin release, while higher doses of BPA did not. In fact, BPA treatment inhibited adiponectin release at a dose 100 times below the current average body burden of an American. At higher doses, BPA did not have an inhibiting effect on adiponectin levels, indicating that low-doses can be more relevant than higher doses, and that simple high to low dose effect extrapolation is inappropriate for environmental hormones with such properties.

<u>These findings are important because:</u>

(1) Humans are widely exposed to BPA at doses which can induce adverse effects in animals and in human cell lines.

(2) Adiponectin is chronically reduced in obese persons, and lower adiponectin levels are a risk factor for developing insulin resistance with subsequent type 2 diabetes and obesity.

(3) The increase in obesity is hypothesized to be linked to environmental pollutant exposure, e.g. to BPA and other xenoestrogens (DES). This has been shown in animal experiments.

In summary, there is extensive scientific data to show that widespread human exposure to BPA at current levels might be a cause of several medical conditions currently observed in humans (Table 2).

Table 2: Effects that have been seen when animals were exposed to low doses of BPA and comparison to currently observed trends in human health (reproduced from (vom Saal 2009)).

BPA effects in mice and rats		Human health trends
Prostate hyperplasia and cancer Mammary hyperplasia and cancer	**Cancer**	Prostate cancer increase Breast cancer increase
Abnormal urethra/obstruction Sperm count decrease Early puberty in females Ovarian cysts/uterine fibroids Abnormal oocyte chromosomes	**Male and female reproductive system**	Hypospadias Sperm count decrease Early sexual maturation PCOS/uterine fibroids Miscarriage
Body weight increase Insulin resistance	**Metabolic disease**	Obesity increase Type 2 diabetes
Hyperactivity/impaired learning Abnormal play behavior Abnormal socio-sexual behavior	**Brain and behavior**	ADHD Autism

Chemicals and Mixture Toxicity

Currently there are over 70'000 synthetic industrial chemicals in use today and more than 2200 chemicals are produced exceeding 1Mio lbs per year in the US. Only a fraction has been tested for their toxicity (Guyton, Kyle et al. 2008). People thus are exposed to a complex mixture of chemicals, some of which are unknown for their toxic properties.

In 2002, an important study was published concerning the toxic potential of chemical mixtures. In their research, the authors from the University of London tested 8 xenoestrogens for their ability to mimic biological effects of the natural hormone estrogen ('estrogenicity') in *in vitro* test system using yeast cells (Silva et al. 2002). When the xenoestrogens were tested individually at low concentrations the measured 'estrogenicity' was very low or undetectable. If these 8 compounds were all present in a mixture at these low concentrations one could assume that their effects would add up to a very low effect, too. However, when tested in practice, the mixture of these 8 xenoestrogens at low dose exerted a strong effect far beyond what could be expected from the individual chemicals' responses. This shows that we must assess the risk of chemicals in their context in which people are exposed to them, not only for the single substances.

This issue of mixture toxicity has also been studied in animals. It is known that mixtures of similarly acting chemicals can have a greater effect than if the chemicals are tested on their own, at the same concentrations. For example, male rats normally do not have nipples. When pregnant rats are exposed to certain compounds their male offspring can be born with nipples, an indication of de-masculinization or reduced manliness by these chemicals that have other effects, too. Growth of some few nipples is seen for the individual compounds and it increases for higher doses or mixtures of these substances. For instance a group of plastic additives called phthalates has this effect {Howdeshell, 2007 #1857}.

Fetal Exposure as Starting Point for Adult Chronic Diseases

The human fetus is exquisitely sensitive to chemical influences. During organ development, lack of nutrition and exposure to endocrine disrupters can have permanent adverse effects, for instance on the heart, brain, and reproductive organs. Environmental hormones are hypothesized to "reprogram" important body functions in the developing human, like immune response or fat storage.

From the synthetic estrogen DES, pharmaceutically used during the 1940s to 1970s, it is well known that fetal exposure to this synthetic estrogen can have detrimental effects later on in adult life. DES is a good, albeit very tragic example, where pregnant women were given known doses of a xenoestrogen, and effects were followed-up in their sons, daughters, grandsons and granddaughters. In fact it is the only such human cohort study of xenoestrogenic exposure during this period of development.

In women that were exposed to DES as fetuses there is an increased risk for several medical conditions, including breast cancer. Mice that were treated *in utero* with low doses of DES became obese as adult animals (Photo) (Newbold, Padilla-Banks et al. 2007).

Photo: Two genetically identical mice of the same age that received the same food, exercise and treatment. The difference is that one's mother was exposed to the synthetic estrogen DES during pregnancy at low doses. This animal is obese when it reaches adulthood. (reproduced from (Newbold et al. 2007)).

Breast Cancer

One in ten of all new cancers diagnosed worldwide each year is cancer of the breast, and it is the most common cancer in women in both developing and developed countries. It is also the principal cause of death from cancer among women globally and its incidence is increasing. In the US there was a 40% increase between the early 1970s and late 1990s (Brody and Rudel 2003). Environmental factors are more important than genetic factors, and men can also develop breast cancer.

It has been shown that breast cancer patients have higher levels of persistent environmental pollutants in their breast tissue. Therefore it has been hypothesized that mixtures of environmental pollutants can contribute to breast cancer development (Ibarluzea, Fernandez et al. 2004). Women that were exposed as fetus to the xenoestrogen DES have a significantly higher risk of developing breast cancer than non-exposed women (Figure 7) (Palmer, Wise et al. 2006).

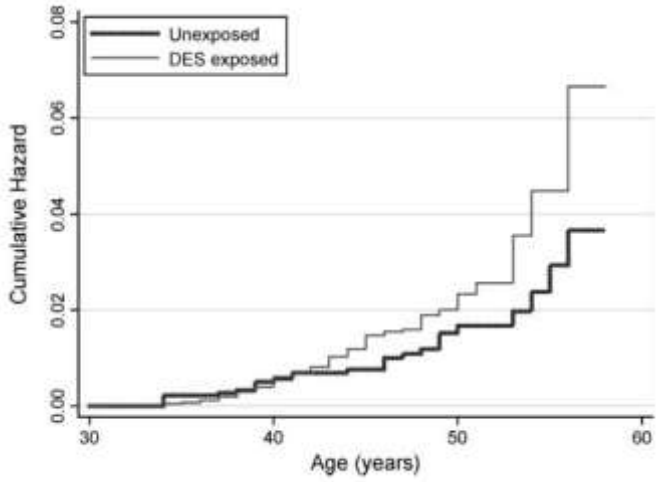

Figure 7: Women have a higher risk of developing breast cancer after age 40 if they were exposed to DES as fetuses, a synthetic estrogen used as pregnancy pharmaceutical. (reproduced from (Palmer et al. 2006))

Estrogenicity of Mineral Waters and Packaging Materials

During the last year, at least three studies were published that looked at total estrogenicity of commercially available mineral waters (Pinto and Reali 2008). For all these studies, samples were obtained from retail in Germany, Italy and the US, respectively. The waters

were analyzed using different test systems, that were all *in vitro* (or: test tube) assays. All samples were shown to be estrogenic, but differed in the extent of estrogenicity.

One study additionally analyzed waters of the same brand, but packaged in different materials (glass, PET and/or laminated carton). When all types of packaging were compared from this extensive data set (over 600 samples for glass and PET analyzed, over 130 samples for laminated carton) it was shown that glass-packaged waters had least estrogenicity, while it was highest in the plasticized carton containers (Figure 8). Estrogenicity of mineral waters could be a result either of chemicals leaching from the packaging, reflect pre-filling contamination from the source, or be a result of pre-filling storage conditions.

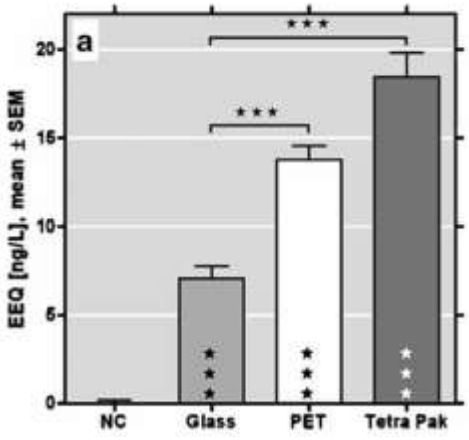

Figure 8: Estrogenicity of mineral waters, packaged in different types of packaging material. The effect – mimicking the natural hormone estrogen – is measured as "estrogen equivalents EEQ", also called estrogenicity. The packaging types analyzed are glass, polyethylene terephthalate (PET) and laminated (plasticized) beverage carton. In all mineral waters estrogenicity was statistically significantly increased compared to the negative control (NC) (reproduced from (Wagner and Oehlmann 2009))

In a second experiment, influence of packaging material itself on estrogenicity was investigated. For this purpose, aquatic snails were kept in either glass or PET mineral water bottles of the same brands. Growth of embryos is an estrogen-sensitive endpoint in these animals. A positive control using a synthetic estrogen (ethinylestradiol, EE2) led to significantly increased embryo growth compared to the negative control (NC). This was also observed for PET-cultivated snails, but not in the animals living in the glass bottles (Figure 9).

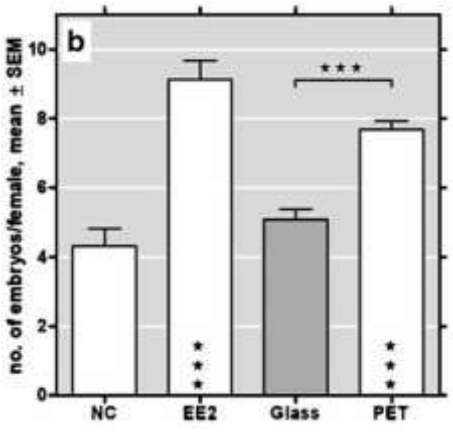

Figure 9: Estrogenicity of mineral water packaging materials. Snails that lived in glass or plastic (PET) bottles were analyzed for their number of embryos after 8 weeks. The positive control ("EE2") is a widely used xenoestrogen. The number of embryos is significantly increased in the positive control and in PET-bred animals, compared to the negative control ("NC") but not in glass-living snails. This indicates that the packaging material is a source of mineral water estrogenicity. (reproduced from (Wagner and Oehlmann 2009))

This research shows that mineral waters possess varying levels of estrogenicity, and that this estrogenicity also depends on the packaging material used. PET packaging is a source of estrogenic compounds. A next step will be to identify all the sources of xenoestrogens in mineral waters and their individual contribution to overall estrogenicity, as well as their chemical structures. In particular, the chemical identity of xenoestrogens originating from PET is of interest.

Genes, Chemical Pollutants, and Chronic Diseases

Traditionally, genes were thought to be the main determining factor for the development of heritable chronic diseases. Today it is clear that environmental influences (food, air, water, social factors, etc.) determine to a larger extent if a disease actually develops or not. Most interestingly, these environmental influences do not necessarily change the gene sequence, but they can affect when a gene is turned on or off, how strongly it is activated and in which parts of the body it is active. This highly complex process can be compared to an aero plane – the plane will only fly if the right switches are activated at the appropriate time. In the cell, these switches are marks on the genes; they do not influence the gene sequences as such. These switches can be damaged by chemicals, and this damage can be passed on over several generations. Thus, epigenetics (meaning "on the gene") is the study of heritable changes in *gene expression* that occur without a change in *gene sequence* (Dolinoy et al. 2007).

Given the complexity of gene expression, the meaning of correct and exact timing when genes are active and when they are silent is highly relevant. However, understanding of these mechanisms currently is fairly limited. New experimental methods will facilitate the study of epigenetics.

In a recently published study, female mice were exposed to different pesticides during the early stage of pregnancy. This exposure affected epigenetic marks – "the switches" – on the genes which lead to a change in gene expression. The exposed mice's male offspring, when they were adults, had sperm of bad quality compared to mice from unexposed mothers, but their genes were identical. This effect even was observed up to 3 generations later, even though the animals were not subjected to further exposures (Anway et al. 2005).

Currently it is not clear which chemicals affect the gene switches. The most vulnerable time for exposure is in early pregnancy, but also before when the reproductive cells (in women: human eggs (oocyte), in men: sperm) are being formed. However, also during adult life factors like diet and chemical exposure are thought to influence the gene switches, thus possibly leading to chronic disease development. An increased understanding of this gene – environment interaction will help in the prevention of chronic diseases.

21st Century Toxicology

In conclusion, the new toxicology paradigms show that chronic diseases are not only dependent on what kind of genes someone has, but also on the environment a person lives in and their lifestyle. Consequently, Paracelsus toxicology of "the dose makes the poison" needs to be updated to reflect our current knowledge of chronic disease pathogenesis by integrating aspects of:

1.) Low dose effects of endocrine disrupters (environmental hormones)
2.) Mixture toxicity
3.) Chemical exposure during fetal development (Developmental Origins of Adult Disease Hypothesis)
4.) Effects of chemicals on how, when and in which organs genes are active (Epigenetics)
5.) and possibly other, so far unknown aspects.

From studying human blood and urine samples it is known that people widely are exposed to a veritable cocktail of industrial chemicals. It is also known that several chronic diseases are increasing. The question is: Does life-long human exposure to a mixture of different chemicals cause chronic diseases (Figure 10)? The answer to this most urgent question is very difficult to give and will take many more years of research to find. Until then a personal precautionary approach is to reduce exposure to chemicals that are not known to be safe.

"It is possible that hormone disruption could pose a more imminent threat to humankind than climate change" (Dr. Theo Colborn, co-author of Our Stolen Future and founder of TEDX-the Endocrine Disrupter Exchange http://www.endocrinedisruption.com).

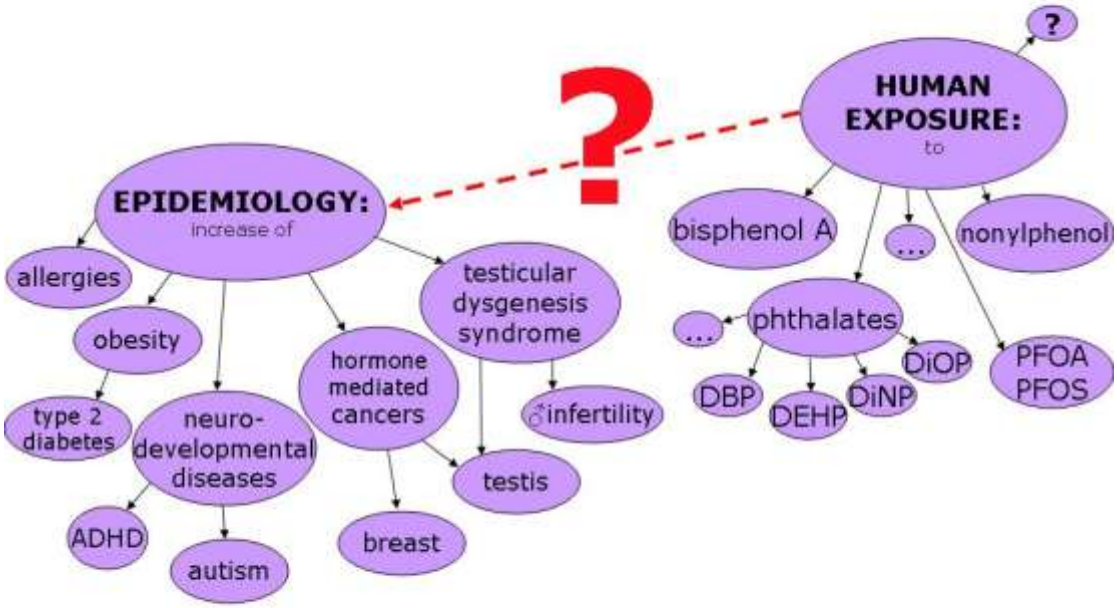

Figure 10: Many different industrial chemicals have been detected in human blood and urine samples, including the plastic food packaging associated substances bisphenol A, phthalates, nonylphenol and perfluorinated compounds. PFOA: perfluorooctanoic acid; PFOS: perfluorooctanyl sulfonate; DBP: di-butyl phthalate; DEHP: di-ethylhexyl phthalate; DiNP: di-isononyl phthalate; DiOP: di-isoctyl phthalate.

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