Superior Health Council

YOUR LETTER DATED 12 February 2013
YOUR REF. MRB/MR/201301

OUR REF. HGR 8914
DATE 17 May 2013

ENCLOSURE(S) -

CONTACT Marleen Van den Brande
PHONE 02 525 09 44
FAX 02 525 09 77
E-MAIL marleen.vandenbrande@gezondheid.belgie.be

Ms. Laurette Onkelinx
Minister of Social Affairs and Public Health
Hertogstraat 59-61
1000 Brussels

SUBJECT : Request for an urgent advisory report on endocrine disrupters.

Dear Minister,

On 13 February 2013 the Superior Health Council (SHC) received your request for an advisory report concerning the issue of endocrine disrupters in the light of the on-going discussions on the European level in order to regulate these substances in several legislative frameworks such as REACH, biocides, cosmetics and toys.

The first part of the request asks for the opinion of the SHC on the WHO definition of endocrine disrupters, and on the use or non-use of the criteria “adversity”, “mode of action”, “relevance”, “potency”, “lead toxicity”, “severity”, specificity” and “irreversibility” for the identification or the characterisation of the danger. The answer is expected for April.

The second question asks whether according to the SHC the scientific elements are sufficient to recognise low dose effects and nonmonotonic dose responses of endocrine disrupters, and which are, following the SHC, the critical windows of sensitivity. The answer to these questions is requested for June,

The SHC wants to express its disappointment about the way in which its opinion is asked. Why was the SHC not consulted in an earlier phase of the process? Discussions on endocrine disrupters are going on already for 15 years or longer and the SHC is consulted only in the final phase of the process, an urgent advisory report being requested now. This is a global, very broad and sensitive issue on which a lot of research has been done and ample international literature exists. Therefore an advisory report of the SHC needs a careful and thorough analysis and consideration of the issue and an in depth examination and summary of the literature. The Council is most willing to contribute, within the bounds

of its possibilities, to the Belgian activities in a constructive way, but in view of the very limited timing the only possibility is to formulate initial comments instead of a constructive and founded support to a Belgian position. So the SHC has the feeling being consulted only “pro forma” and insists to be involved in the future during an earlier phase of the process.

The first question was treated by experts in endocrinology and discussed in the permanent working group of the SHC on chemicals. This advisory report refers to the adverse health effects of endocrine disrupters.

In general the Council focuses on the limiting interpretation of the definition of “endocrine disruptors” as provided in the documents at stake. The Council understands that stakeholders as industry aim limiting tests at a level which is financially acceptable. On the other hand, from a scientific and a public health point of view, it is advisable widening the scope of endocrine disruptors to substances and mixtures for which scientifically sound laboratory evidence has been developed. The Council wants to avoid that a too limiting definition excludes in beforehand groups of products or pollutants which might offer a hazard to public health.

The present comments refer to a recent EU report (*extracts in italics*) on the protection of public health from endocrine disruptors (2012/2066(INI)) that was voted by the European Parliament on 13 March 2013.

Definition from the WHO/IPCS (2002) report: "An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations." A potential endocrine disruptor is "an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub)populations." (http://www.who.int/ipcs/publications/en/ch1.pdf).

(-)The **endocrine system** includes any cell in the body producing and releasing chemical mediators (the hormones) for action on other cells through specific receptors. Originally, the hormones were thought to be only produced by endocrine glands and to be released into the circulation to act away from their sites of origin. Now, it is recognized that hormone-producing cells are not only located in endocrine glands but also in other tissues (e.g. the stomach and the adipose tissue) and that their action can also take place in the vicinity of their site of origin. It is important that the endocrine system is viewed in such a broad sense in the perspective of endocrine disruption.
(-)The definition mentions not only individual substances but also **mixtures**. This is most relevant from an environmental point of view because, except accidental toxic spills exposing to high doses of a single chemical (“Seveso”), humans are most commonly exposed to low doses of several chemicals together. Different environmental media (e.g. sludge of different types) and mixtures of pollutants (e.g. pesticides) were shown having endocrine disrupting properties. The issue is rather complex since as experience from the past (e.g. on biocides or vegetation protection substances) showed, difficulties in developing strategies analyzing the hazards of these mixtures exist. More importantly, the approach for testing by industry and legislating by authorities has been so far oriented towards individual chemicals.

(-)The definition equally refers to **intact organisms**. With regard to this approach the Council wants to stress that *in vitro* testing including the use of micro-organisms with reporter genes is useful but complementary to the *in vivo* approach. While evidence of effects *in vitro* is highly suggestive of endocrine disruption, absence of effects does not exclude endocrine disruption because several parameters such as critical windows of sensitivity and interaction with endogenous endocrine system are not included. Although it is recommended to limit animal testing, and in that case the advice of the ethical council dealing with animal maltreatment is most indicated, it can be inadequate to rely on only one approach.

"6. Stresses that it is essential to base the criteria to determine endocrine disrupting properties on a comprehensive hazard assessment carried out on the basis of state of the art science, taking into account potential combination effects as well as long-term effects and effects during critical windows of development; the hazard assessment should then be utilized in the risk assessment and risk management procedures as prescribed in various relevant legislation;"

Importantly, according to the above WHO definition, a **potential endocrine disruptor** is an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action. When such interference leads to hazard, the chemical becomes effectively an **endocrine disruptor** requiring risk assessment. Thus the conditions of screening for hazard identification are critical including the selected endpoints, the age window of exposure, the latency between exposure and effects, the frequency of exposure, the dose of chemicals and the possible mixture effects, among other parameters. Therefore the word *comprehensive* hazard assessment is crucial.

"8. Takes the view that the criteria for defining endocrine disruptors should be based on criteria for defining 'adverse effect' and 'endocrine mode of action'; the WHO/IPCS definition being the appropriate basis for that purpose; considers that both 'adverse effect' and 'endocrine mode of action' must be examined and weighed up in parallel in a comprehensive assessment; considers that observed effects should be assumed to be harmful if there is scientific data to indicate this; stresses that any possible combination effects such as mixtures or cocktail effects should be taken into consideration;"

(-)**Adversity** is linked with harm caused by an endocrine disruptor as an outcome of interference with hormone action that is the **mode of action.** While adversity of effects is a component of the definition, the endocrine mode of action provides weight of evidence of endocrine disruption. **Adversity** is meant as any non-physiological observation i.e. that is beyond the "normal" variations within a population. Depending on the conditions (e.g. sample size, cross-sectional versus longitudinal studies) and the endpoint, the normal limits can be adjusted; e.g.: abnormal adiposity can be defined as a BMI > 90th centile (overweight) or > 97th centile (obesity). In an animal study, it will be defined as adiposity different from a control group. Adversity should not involve any reference to severity because an apparently benign effect occurring first in life can increase the likelihood of other more severe effects occurring subsequently; e.g.: a reduced ano-genital distance in males at birth is a non-severe adverse effect that can be associated with severe effects later in life such as reduced sperm count and testicular cancer.
In relation to endocrine disruptors specific attention should be given to intrauterine

exposure.
Moreover adversity in relation to health effects is value loaded. Over the past decades it proved hardly possible determining objective criteria which define "adverse" health characteristics. In relation to endocrine disruptors specific attention should be given to pre-symptomatic effects providing an indication for the likelihood of disease.
(-)On the basis of the present understanding and experimental evidence all chemicals that bind specifically to cell receptors could in some way contribute to endocrine disruption. This implies that data on *in vitro* binding to receptors followed by activation or blocking are certainly relevant. All chemicals binding to receptors at relevant concentrations should be considered potential endocrine disruptors The **endocrine mode of action**, however, implies that endocrine disruption follows the *in vivo* principles taken from fundamental endocrinology with complex mosaic effects produced through simultaneous actions or a cascade of effects in different tissues with changing sensitivity throughout the life cycle. Moreover these complex events occur at very low concentrations (parts pro billion – ppb); often no threshold dose can be determined. It is very important that scientific studies on the modes of action of endocrine disruptors are pursued. However, while evidence on the endocrine mode of action adds to the demonstration that a chemical is an endocrine disruptor, it is not required according to the definition but useful for characterization. Furthermore, emphasis has been put in the past on sex steroids and thyroid hormones in characterizing the endocrine mode of action of endocrine disruptors. It is now recognized that other endocrine systems or mechanisms can be involved as well. Of major importance is that endocrine disruptors not only act through the classical nuclear receptors, but also through membrane-bound receptors, through estrogen-like receptors, through cytoplasmic interactions, through cross-talk between genomic and non-genomic pathways, and that effects of activation of receptors differ in function of the ligand.

"25. Stresses that current science does not give sufficient ground for setting a limit value below which adverse effects do not occur and therefore endocrine disruptors should be regarded as 'non-threshold' substances, and that any exposure to such substances may entail a risk, unless the manufacturer can show scientific proof that a threshold can be identified, taking into account increased sensitivities during critical windows of development, and the effects of mixtures;"

Low-dose effects and **non-monotonic dose responses** have been proven for some endocrine disruptors and should be considered as a possibility for any potential endocrine disruptor until evidence of no such effects is provided using low to very low doses (usually in the range of human exposure). This issue is challenging the classical concepts of toxicology based on thresholds below which exposure should not cause any adverse effect. This is also challenging the screening programs since they tend towards reduced number of tested doses in a single condition that could not be in the **window of highest sensitivity** for endocrine disruptors. Evidence is accumulating that prenatal and early postnatal periods are crucial for the fetus establishing regulation of essential body functions. This organizing phase will determine homeostasis of processes such as control of energy balance and reproduction for the entire life under the influence of physiological environmental factors including nutrition and stress as well as non-physiological factors such as endocrine disruptors. Women before and during

pregnancy and young children are thus a priority concern. The issues of low dose effects and critical windows of sensitivity cannot be addressed separately since they are central in the demonstration that a chemical is or is not an endocrine disruptor.

Sincerely yours,

On behalf of the Superior Health Council,

André Pauwels,
CSS Coordinator

The following experts were involved in drawing up the advice:

- Mr. ADANG Dirk (environmental health - UCL)
- Mr. BOURGUIGNON Jean-Pierre (pediatric endocrinology - ULg)
- Ms. CHARLIER Corinne (toxicology - ULg)
- Mr. DEMOULIN Vincent (ecotoxicology - ULg)
- Ms. DIRINCK Eveline (endocrinology – UZA)
- Mr. HENS Luc (human ecology - VITO)
- Mr. STEURBAUT Walter (human exposure - UGent)
- Mr. VAN GAAL Luc (endocrinology – UZA)
- Ms. VANHAECKE Tamara (toxicology - VUB)
- Mr. VAN LAREBEKE-ARSCHODT Nicolas (toxicology, cancer - UGent)
- Mr. VERSTEGEN Geert (toxicology - Antigifcentrum)