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**'Environmental Oestrogens':
Male Reproduction and
Reproductive Development**

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ECETOC TASK FORCE ON 'ENVIRONMENTAL OESTROGENS'

'ENVIRONMENTAL OESTROGENS' : MALE REPRODUCTION AND REPRODUCTIVE DEVELOPMENT

The following position paper was developed in a subgroup of the main task force (Appendix 1) assigned with the task of reviewing the existing reviews of the currently available data relevant to the putative effects of chemicals on human male reproductive health.

The paper, which has been reviewed by the main task force and the Scientific Committee (Appendix 2), describes the current state of knowledge and outlines a strategy for resolving the uncertainties. It has been produced to provide briefing for member companies.

"Where are we ?"

A hypothesis that "environmental oestrogens" can be linked to the epidemiological evidence suggesting changes in human sperm counts and/in male reproductive development has received great attention in the press and by various government agencies in the UK, Denmark, USA and Germany.

The hypothesis (first published by Sharpe and Skakkebaek, 1993) postulates that the exposure to "oestrogens" of the foetus *in utero* or neonates in the early lactation period, when testicular Sertoli cells are undergoing division and differentiation, can be related to the incidence of human reproductive disorders:

viz

1. Decreasing sperm count;
2. Increasing incidence of testicular cancer;
3. Increased incidence of cryptorchidism (testicular maldescent) or,
4. Hypospadias (congenital malformation of the penis)

This proposed hypothesis suggests that the differentiation of the Sertoli cell plays a key role. Sertoli cell replication and differentiation is under the control of the gonadotrophin, FSH. Once Sertoli cells have completed their round of division and their numbers established (day 16 *post partum* in the rat), the testicular complement will not be increased. Since Sertoli cells will provide a "nurse" function to a fixed number of germ cells, any reduction in Sertoli cell number will lead to a decrease in sperm output/count on reaching adulthood, but with no histopathological evidence of seminiferous epithelial damage. Sertoli cells in the foetal testis also secrete a hormone, Mullerian Inhibiting Substance (MIS), involved in the regression of the female reproductive vessels (the Mullerian ducts) and facilitating transabdominal descent of the testis (ie failure in this process could lead to cryptorchidism). Factors from the Sertoli cells are also involved in the control of germ cell replication, including potential carcinoma *in situ* (CIS) cells (ie malfunction could lead to testicular cancer due to an increased production/replication of CIS cells). Sertoli cells in the pre-pubertal testis also secrete natural oestrogens which regulate negatively Leydig cell development. Leydig cells are the primary source of testicular androgen. A reduction in Leydig cells will reduce testosterone output and thus impair transinguinal descent of the testes (cryptorchidism) and masculinization of the reproductive tract (hypospadias).

The evidence supporting or refuting this hypothesis has been extensively reviewed and published in recent government reports (eg Danish EPA, 1995; UK MRC, 1995). Much debate still exists in the scientific community on the validity of the proposed hypothesis and whether the changes in male reproductive health claimed are supported by reliable figures/diagnoses. Certain authors have advised that more caution should be employed in the interpretation of the epidemiological data due to methodological problems etc.

The balanced view of the debate, however, would be that there is sufficient evidence to cause concern with regard to male reproductive health/development, but that the data available are not sufficient or definitive.

In terms of the hypothesis proposed by Sharpe and Skakkebaek (1993), this is scientifically plausible, based on animal models (and some human studies) indicating that pharmacological agents (eg Diethyl stilbestrol (DES), supraphysiological doses of oestradiol, decreased FSH) will affect fertility and reproductive development. However, there are **no published data** indicating that exposure to "environmental" oestrogens (or other endocrine modulating chemicals) under **relevant** exposure conditions will lead to the production of adverse reproductive effects.

A recent (as yet unpublished) paper by Sharpe *et al* (1995), has indicated that a number of proposed "environmental" oestrogens (eg butyl benzyl phthalate, octyl phenol) will, in a rat animal model with low level exposure during the critical period described above, produce deficits in male offspring in terms of testicular size and daily sperm production rate. Because of uncertainties over the design of the studies and the outcome observed, there is a need to develop further experience of such experimental approaches. Indeed these data, though they are consistent with the proposed hypothesis, remain to be confirmed and **do not indicate that the deficits noted are due to an effect by an oestrogenic mechanism.**

Note: For the purposes of discussion, the work group defined an ENDOCRINE MODULATOR as a substance that affects adversely the hormonal control of reproductive systems

"Where do we want to be ?"

The WG propose that the following actions are required to focus refine and test the suggested hypothesis that ambient exposures to certain environmental chemicals can discernably modify male human reproductive function or development.

1. Ensure a coordinated assessment and response from all interested industries to the presumed problem. The first and most important step is to develop effective liaison between organizations such as ECETOC, Chlorine Chemistry Council (CCC) and American Industrial Health Council (AIHC) in Europe and North America. This will serve to identify common ground and provide the basis for agreement on principal issues.
2. Accept that the presumed problem may fragment into two different streams - receptor mediated effects (molecular/cellular) and hormone modulating/disruption effects (functional/whole organism). Data from these separate compartments will have different inputs to human risk assessment.
3. Distinguish between research (information) needs for chemicals that already have large relevant toxicological databases that may need supplementation (eg pesticides), from those which have no, or minimal, relevant data.
4. Identify assays/protocols and testing hierarchies to use with agents having inadequate data (testing using model agents).
5. Initiate or support research aimed at testing the basic hypothesis of the problem, and when appropriate, further understand the problem. The main areas identified are:
 - (i) Prospective epidemiology of human reproductive function among males exposed to defined agents or mixtures possessing indicative reproductive toxicology data from experimental systems. [(i) and (ii) are

regarded as outwith the scope of industry without the support of National and International Health Organisations].

- (ii) Assessment of the relative contribution of lifestyle and naturally occurring endocrine modulators (eg phytoestrogens) in comparison with synthetic chemicals.
 - (iii) Identification of the test data and dose response data most suited to human risk assessment.
 - (iv) Consideration of the concept of thresholds as applied to receptor interactions and functional deficits, using model agents.
 - (v) Consideration of how to model human exposure *in utero*, including consideration of biological persistence, rates of detoxification and differences between rodent and human placenta, etc.
 - (vi) Consideration of synergistic, additive and/or antagonistic effects operating for mixtures of active agents.
6. Identify centres of experimental excellence, both industrial and academic, and possible sources of research funding. Data alone will influence this debate. Therefore, the most urgent need is to identify industrial laboratories generating or intending to generate data relevant to this topic. This will enable redundancy of effort to be avoided, complementarity to be encouraged and chemical selection to be discussed.
7. Harness data and concepts with a view to encouraging objectivity in those developing scientific and regulatory policy in this area.
8. Maintain a list of agents suggested to have endocrine modulating activity, the list broadly stratified from molecular events to functional effects. Assessment

of this list could yield agents for study whose activity *in vitro* is unlikely to be expressed in mammals. Publication of such data could deter over-reliance on *in vitro* data.

In the first instance, the work group recommend the following action plan with a view to a) determining the validity of the above proposals; b) enhancing the scientific credibility of the chemical industry in this area of research; and c) to lay the foundations for future meaningful collaborations with academia and regulatory agencies.

1. Identify Companies with research facilities and/or recognized practical expertise in reproductive/endocrine modulation toxicity.
2. Identify all ongoing programmes of experimental work addressing this topic within industry.
3. Ask these Companies to nominate up to 2 scientists who would be willing to participate in a workshop (see 4 below).
4. Establish a small organising committee from members of the Environmental Oestrogens Task Force to plan and manage a workshop to be held in January/February 1996 at ECETOC. The workshop objectives will be to critique the outline research areas noted above and to make recommendations with regard to which aspects of the proposals could be undertaken in our own (industrial) laboratories and to include cost, time frames etc.

REFERENCES

Danish EPA (1995). Male reproductive health and environmental chemicals with estrogenic effects. Miljøprojekt Nr. 290.

Sharpe RM and Skakkebaek NS (1993). Are oestrogens involved in failing sperm counts and disorders of the male reproductive tract. Lancet 341:1392-1395.

Sharpe RM, Fisher JS, Millar MM, Jobling S and Sumpter JP (1995). Gestational/neonatal exposure of rats to environmental oestrogenic chemicals results in reduced testicular size and sperm production in adult life. Environ Health Perspec. (in press).

UK MRC, Institute for Environmental Health (1995). IEH assessment on environmental oestrogens: consequences to human health and wildlife. UKMRC.

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