Parma, 20 March 2013

Notes to editors

Background:

The endocrine system is important for human and animal health because it regulates and controls the release of hormones that are essential for functions such as metabolism, growth and development, sleep and mood. The endocrine system is very complex; the feedback loops which regulate hormonal release are dependent on a variety of biological and physiological factors and our knowledge of it is still growing. Exposure to endocrine active substances during critical stages of development (for instance, conception, pregnancy, infancy, childhood and puberty) when the body may be more sensitive to certain hormonal activities, could increase the likelihood of harmful effects in the short-term or later in life. Humans and animals may be exposed to a wide range of endocrine active substances through the diet as well as other sources. Endocrine active substances can be naturally-occurring (such as phytoestrogens in soya) or man-made (like some pesticides or pollutants). Some endocrine active substances are purposefully used in medicines for their endocrine active properties (e.g. birth control pills, substitutes for thyroid hormones).

The World Health Organization (WHO) defines an endocrine disruptor as follows: "…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." Through the International Programme on Chemical Safety (IPCS), the WHO works to establish the scientific basis for the sound management of chemicals, and to strengthen national capabilities and capacities for chemical safety.

The harmonisation of the testing of chemicals has been an ongoing activity of the Organisation for Economic Co-operation and Development (OECD) since the 1980s. A core activity on endocrine disrupters was initiated in 1997 and under this umbrella both specific tests and a conceptual framework for such tests have been developed. EFSA cooperates with the OECD in a number of such activities.

Hazards versus risks – Whether an endocrine active substance represents a hazard (that is, can be considered as a potential endocrine disruptor) is related to its inherent ability to interfere with the endocrine system and consequently cause an adverse effect. A *hazard* is a possible threat related to the intrinsic properties of a substance (for example its toxicity may be shown to cause cancer). The *risk* that the endocrine disruptor could cause harm, resulting in adverse effects in humans and animals depends on the degree (dose), duration and timing of exposure to this hazard for humans or

animals. Hazards may not be of concern if there is no exposure to them, or exposure is too low to cause harm. For example, amygdalin is a substance present in the stone of apricots. As a chemical it is quite toxic and therefore a hazard. But because we do not generally eat the stone, the consumer is not exposed to it and therefore we consider that the risk to the consumer from consuming apricots is low. This is also the case for endocrine disruptors. Assessing whether it is likely that a substance, in this case an endocrine active substance, will cause harm at a given or predicted exposure and what would be an exposure of no concern are the goals of risk assessment.

Further details about EFSA's new opinion:

Definition and identification of endocrine disruptor **-** The Scientific Committee endorses the WHO definition that an endocrine disruptor is defined by three criteria: the presence of an adverse effect in an 'intact organism' (relevant for mammals) or (sub)population (for wildlife in the ecosystem); the presence of endocrine activity; and a plausible causal relationship between the two. There are no specific scientific criteria defined to distinguish potential adverse effects of endocrine disruptors from normal regulation of body functions (so-called 'adaptive responses'). Experts need to assess the weight of available evidence on a case-by-case basis for each substance.

Test methods for identifying endocrine active substances – EFSA experts thoroughly examined (internationally) standardised test methods for the identification of endocrine active substances. They concluded that a reasonably complete set of 'assays' (tests or trials) is or will shortly be available to cover adequately those parts and pathways of the endocrine system in mammals and fish currently known to be sensitive to endocrine disruption, but with fewer tests available for birds and amphibians. The hormone pathways best addressed by testing methods relate to oestrogen, androgen and thyroid hormones as well as steroidogenesis (the biological process for production of steroid hormones). In principle, no single test is likely to provide all the information needed to decide whether a substance is or is not an endocrine disruptor. One reason for this is that tests are generally designed to ascertain either endocrine activity or different types of adverse effects, but not both.

Issues not unique to endocrine active substances **-** EFSA's experts stated that critical windows of susceptibility, combined exposure to multiple substances, and non-monotonic dose-response relationships (e.g. U-shaped[1]) should be considered across the spectrum of various substances. The opinion notes the lack of international consensus on the existence/relevance of so-called 'low-dose effects'. EFSA therefore cannot conclude whether the current test methods are adequate to fully define dose-response relationships for endocrine disruptors. On a case-by-case basis, if triggered by unusual findings, an extended dose-response analysis of doses administered at wider ranges could be performed. EFSA also considers that adverse effects occurring at the

[1] Non-monotonic dose-response curves are produced when the response to a substance increases with the dose at some points and decreases as the dose increases at others.

lowest observable effect level should continue to be used to guide safety assessments, whether due to endocrine activity or another toxic effect. This will protect against other possible endocrine-related effects at higher doses.

***Future action on EAS*:**

Where the Scientific Committee has identified gaps in the current toxicity testing methods for endocrine active substances, EFSA makes recommendations for future activities and development of test methods.

The Scientific Committee underlined the need for further testing strategies to be developed to test these substances in a systematic and transparent way. These strategies should generate the data adequate for the assessment of possible endocrine disrupting properties.

EFSA recommends as a follow up to clarify in a broader context how the issues of thresholds and criteria for adversity (i.e. what is an adverse health effect vs. what is an adaptive response), combined exposure to multiple chemicals and non-monotonic dose response relationships could impact on current hazard and risk assessment approaches and testing strategies.