

CODEX ALIMENTARIUS COMMISSION



Food and Agriculture
Organization of the
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World Health
Organization

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Discussion Paper on the Uniform Risk Management approach to address the issue of Endocrine Disrupting Chemicals in Food

(Prepared by India)

Introduction

1. One of the strategic objectives of the Codex Alimentarius Commission (CAC) is to proactively identify emerging issues and members' needs, and where appropriate, develop relevant food standards.

Purpose

2. The purpose of this discussion paper is to develop an internationally acceptable broad-based definition of Endocrine Disrupting Chemicals (EDCs) in the context of food safety, and to develop a risk based guidelines to deal with their presence in food products.

Background

3. Over the years, increasing reports of diseases like cancer, hormonal imbalance and fertility issues among humans has led to the identification of certain chemical substances interfering with the hormonal system and their linkage with these diseases. These chemicals which may affect endocrine system can be classified as Endocrine Disrupting Chemicals (EDCs). As per World Health Organization/International Programme on Chemical Safety (WHO/IPCS, 2002) endocrine disruptor is defined as "an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse¹ health effects in an intact organism, or its progeny, or (sub) populations." And, potential endocrine disruptor is defined as "an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism², or its progeny, or (sub) populations³".
4. EDCs encompass a variety of chemical classes, including **pesticides**, natural and synthetic hormones, plant constituents, compounds used in the plastics industry and in consumer products, and other industrial by-products and pollutants.

Endocrine disrupting chemicals can be categorized into three groups i.e. pesticides (e.g. (DDT, chlorpyrifos), chemicals in products (e.g. phthalates, triclosan), and food contact materials (e.g. Bisphenol A)⁴. EDCs have been suspected/alleged to be associated with altered reproductive function in males and females; increased incidence of breast cancer, abnormal growth patterns and neuro-developmental delays in children, as well as changes in immune function without any weight based evidence.

¹ Adversity" is defined as "a change in morphology, physiology, growth, development or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increased susceptibility to the harmful effects of other environmental influences (WHO/IPCS 2004)

² The term "intact organism" is understood to mean that the effect would occur in vivo, either observable in a test animal system, epidemiologically or clinically. However, it does not necessarily mean that the adverse effect has to be demonstrated in an intact test animal, but may be shown in adequately validated alternative test systems predictive of adverse effects in humans and/or wildlife.

³ State of the Science of Endocrine Disrupting Chemicals (WHO, 2002)

⁴ A review on endocrine disrupting chemicals and their possible impacts on human health; Eva Rahman Kabir, Monica Sharfin Rahman, Imon Rahman; Environmental Toxicology and Pharmacology

5. The data linking exposures to EDCs and human diseases are much stronger now than in 2002. Since human studies can show associations only, not cause and effect, it is important to use both human and animal data to develop the evidence for a link between exposures to EDCs and human disease. Even so, it may never be possible to be absolutely certain that a specific exposure causes a specific disease or dysfunction due to the complexity of both exposures and disease etiology across the lifespan. Over the past 10 years, there has been a dramatic shift in focus from investigating associations between adult exposures to EDCs and disease outcomes to linking developmental exposures to disease outcomes later in life. This is now considered the most appropriate approach for most endocrine-related diseases and dysfunctions⁵.
6. There is a need to harmonize guidance on the regulation of EDCs, but this has been hampered by what appeared as a lack of consensus among scientists due to following scientific uncertainties:
 - a) Certain hormones interact with their receptors according to an equilibrium reaction. Accordingly, the concentrations of both free hormone and free receptor are important variables controlling hormone action, explaining why different cells and tissues at different times during development are differentially sensitive to the hormone.
 - b) Threshold- It is possible that thresholds do not exist; the reason of the uncertainty is the limitation of the experimental constraints and the understanding of the biology. It is not possible to define thresholds only by experiments in whole organisms due to lack of sensitivity. The existence of thresholds must be defined by understanding better the mechanisms of action in a quantitative systems approach.
 - c) Non-monotonic effects do exist for some EDCs in vitro or in vivo. The question is how often adverse non-monotonic effects occur. Non-monotonic effects may derive from different mechanisms working together or against each other
 - d) The currently validated OECD guidelines may not cover all potential adverse effects or modes of action of EDCs. Improved study designs to find possible non-monotonic effects are available, but not yet agreed. More dedicated methods are needed to evaluate possible effects relevant for humans, especially for hormonal cancer induction or long-term effects.
7. Prominent in these disputes was the question of the existence of thresholds for endocrine disrupting chemicals and of the significance of non-monotonic dose–response relationships, which has a significant impact on the way risk assessments are conducted for these chemicals (Dietrich et al. 2013; Bergman et al. 2013).
8. There was an expert meeting of international scientists in Berlin, Germany on 11–12 April 2016. Participants discussed scientific principles for the identification of Endocrine Disruptors (EDs). While highlighting the difficulty in retrospectively reconstructing ED exposure, insufficient range of validated test systems for EDs, and some issues impacting on the evaluation of the risk from EDs, such as non-monotonic dose–response and thresholds, modes of action, and exposure assessment, there were some consensus. (Solecki et al., 2017)⁶
9. Validated screening and testing systems have been developed by a number of governments, and it requires considerable time and effort to ensure that these systems function properly. New approaches are also being explored whereby large batteries of high-throughput in vitro tests are being investigated for their ability to predict toxicity, the results of which may be used in hazard identification and potentially risk assessment. A challenge to moving forward is that EDC research over the past decade has revealed the complex interactions of some chemicals with endocrine systems, which may escape detection in current validated test systems⁵.
10. Finally, it will be important to develop weight-of-evidence approaches that allow effective consideration of research from all levels—from in vitro mechanistic data to human epidemiological data⁵.

Contemporary approaches

11. Globally, regulations of chemical substances are being carried out largely based on risk based approaches. However, regulations of some countries require both hazard and risk based approaches for decision-making to be applied in different ways.
12. A risk-based approach takes into account the exposure assessment of the chemicals. Risk based methods to monitor EDCs both in the environment and in humans include measurements of environmental and tissue concentrations, questionnaires, personal monitoring devices, biomarkers, and mathematical models.

⁵ State of science of endocrine disrupting chemicals 2012; summary of decision makers (WHO, 2013)

⁶ Solecki ,et.al,2017; Arch Toxicol (2017) 91:1001–1006

13. However, a hazard-based approach regulates substances on the basis of their intrinsic properties, without taking account of the exposure to the substance. As per 'Hazard criteria', even a minimal presence of side effects would be treated as unsafe to human health, plant, and wildlife. This approach discards 'tolerable daily intake' of substances. In other words, any inherent presence of risks in the chemical substances would be considered as hazardous. It does not consider the conditions of coming into contact, dosage level, duration of exposure, time of occurrence, in risk management.
14. US- Environmental Protection Agency has developed Endocrine Disruptor Screening Program (EDSP) which uses a tiered approach for screening chemicals. Tier 1 screening data is used to identify substances that have the potential to interact with the endocrine system and those chemical which are found to exhibit the potential to interact with the estrogen, androgen, or thyroid hormone systems will proceed to Tier 2 for testing. Tier 2 testing data identifies any adverse endocrine-related effects caused by the substance, and establish a quantitative relationship between the dose and that adverse effect. The results of Tier 2 testing will be combined with other hazard information and exposure assessment on a given chemical resulting in the risk assessment. Risk assessments are used to inform risk mitigation measures, as necessary and regulatory decisions concerning chemicals⁷.
15. Japan has recognized that it is important to identify the exact harmful effects induced by suspected endocrine disruptors by accumulating the results and data of scientific researches and assessments on the issue in cooperation with relevant authorities, so as to deal with the adverse effects (toxicity) on the basis of appropriate risk assessment⁸.
16. European Union (EU) adopted a regulation EC No. 1107/2009 which brought changes in the regulatory framework of pesticides. In line with established practice in other jurisdictions, the risk management of chemicals in the EU is generally based on risk characterization. However, for some toxicological effects, the EU has introduced hazard-based regulations. This applies especially to chemicals used as active substances in plant protection products and biocidal products. According to provisions in several pieces of EU law for plant protection products and biocidal products, the European Commission was obliged to develop scientific criteria for the identification of EDs. Very recently, it has also notified the scientific criteria as part of its regulation EC No. 1107/2009 by which the chemical substances can be screened for endocrine disruption function and it proposes hazard identification criteria which are based on the WHO/IPCS definition⁹. Therefore, any chemical which is identified as Endocrine Disruptor against the above criteria will not be allowed approval as Plant Protection Product. In other words, any inherent presence of risks in the chemical substances would be considered as hazardous. It does not consider the conditions of coming into contact, dosage level, duration of exposure, time of occurrence, in risk management. Further there are many scientific gaps in regulatory understanding among the global scientific community due to the reasons explained above.

Need to develop guidelines to identify EDCs

17. Any departure from fundamental principles of the scientific risk assessment framework as well as regulatory decision without sufficient scientific weight of evidence approach will remove many crop protection tools from the market, even if these substances have histories of safe use and are still being used safely under risk-based systems. Without conducting scientific assessments to identify actual risks, such approach may do little or nothing to improve public health or the environmental protection, but will almost certainly have significant adverse consequences for sustainable agricultural production, international food trade and food security.
18. Different Risk Management responses by countries in regulating these chemicals including pesticides may not lead to any gains objectively in respect of food safety but could only lead to trade difficulties.
19. There is currently no widely agreed system for evaluating the strength of evidence of associations between exposures to chemicals (including EDCs) and adverse health outcomes. The need for developing better approaches for evaluating the strength of evidence, together with improved methods of risk assessment, is widely recognized.

Therefore, it is necessary to develop guideline which shall facilitate member countries to take risk management decisions to deal with EDCs in order to overcome unnecessary trade barriers.

⁷ <https://www.epa.gov/endocrine-disruption/endocrine-disruptor-screening-program-edsp-tier-1-assessments>

⁸ <http://www.meti.go.jp/english/report/data/g020205be.pdf>

⁹ <http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52016DC0350&from=EN>

20. The Codex Alimentarius Commission (CAC) is ideally placed to consider and promote an internationally harmonized approach for regulators to address possible public health and trade issues when dealing with presence of endocrine disrupting chemicals in food where no Codex or international regulatory framework for risk management is available. CCPR is an appropriate Committee as pesticides, under the category of EDCs, are of major concern from food safety and international trade point of view.
21. A similar work- Development of Risk Management Guidelines to address chemicals inadvertently present in food at very low levels- is already approved by CAC and currently undertaken by CCCF.

Recommendation

22. It is recommended that the CCPR
 - a. Endorse new work on the development of uniform risk management approach to address the issue of Endocrine Disrupting Chemicals in Food; and
 - b. Forward the attached Project Document to the CAC for approval.

Project Document
Uniform Risk Management approach to address the issue of
Endocrine Disrupting Chemicals in Food
(Prepared by India)

1. Purpose

The purpose of this work is to develop internationally acceptable broad-based definition of Endocrine Disrupting Chemicals (EDCs) in the context of food safety, and to develop uniform guidelines backed with robust sound scientific facts which shall facilitate the member countries to take risk management decision on weight of evidence basis for EDCs.

The work will be based on a review of current regulatory approaches and global best practices taking into account risk analysis principles and frameworks.

2. Scope

Development of a uniform risk management approach in respect of chemicals especially pesticides, which may have endocrine disrupting properties present in food.

3. Its relevance and timeliness

Over the years, there has been growing scientific concerns over the potential adverse effects that may occur from exposure to a group of chemicals known as Endocrine Disrupting Chemicals (EDCs) that may have the potential to alter the normal functioning of endocrine system in humans. These growing concerns have been recognized by regulatory authorities around the world and have also stimulated many national governments, international organizations, scientific bodies, and public interest groups to establish research programs, organize conferences/workshops, and form expert groups/committees to address and evaluate EDC-related issues. However, there is no internationally harmonized approach to address this issue which could pose a potential challenge to international trade.

The Codex Alimentarius Commission (CAC) is ideally placed to consider and promote an internationally harmonized approach for regulators to address possible public health and trade issues when dealing with presence of endocrine disrupting chemicals in food where no Codex or international regulatory framework for risk management is available.

4. The main aspects to be covered

The proposed work will review the existing definitions of EDCs and current regulatory approaches for risk analysis of EDCs. Based on best practices available and considering scientific advice, risk based guidelines will be developed to take risk management decisions while taking in to account public health and trade concerns. Both risk assessment and risk management should be guided by predetermined risk assessment policy.

5. An assessment against the criteria for the establishment of work priorities

Criteria applicable to general subjects

a. Diversification of national legislations and apparent or potential impediments to international trade

Globally, regulations of chemical substances are being carried out largely based on risk based approaches. However, regulations of some countries require both hazard and risk based approaches to enable decision-making to be applied in different ways.

Such diversification in fundamental principles of the scientific risk assessment framework as well as regulatory decision will pose unnecessary international trade barriers. Therefore, harmonized regulatory guideline shall facilitate member countries to take risk management decisions to deal with EDCs in order to overcome unnecessary trade barriers.

b. Scope of work and establishment of priorities between the various sections of work

See 1 and 2 above

c. Work already undertaken by other international organizations in this field and/or suggested by the relevant international intergovernmental body (ies)

WHO has published a document titled “State of the Science of Endocrine Disrupting Chemicals” in 2002 expressing concerns in relation to EDCs which have stimulated many national governments, international organizations, scientific bodies, and public interest groups to establish research programs, organize conferences/workshops, and form expert groups/committees to address and evaluate EDC-related issues.

d. Amenability of the subject of the proposal to standardization

The proposed work would draw on the experience gained from current regulatory approaches. Members would benefit from an internationally harmonised risk analysis approach to address the issue of chemicals including pesticides with endocrine disrupting properties present in food.

e. Consideration of the global magnitude of the problem or issue

As noted in this paper, the issue of EDCs present in food is of significant interest to the wider membership of Codex and an internationally harmonised approach will be helpful to:

- Promote a science and risk based approach to responding to such issue
- Promote efficient use of limited global and national risk analysis resources to address chemicals of greatest public health concern;
- Minimise any potential impediments to international trade;
- Enhance risk communication to consumers and promote confidence in national regulatory approaches.

6. Relevance to the Codex Strategic Objectives

The proposed work would contribute to the Commission’s Strategic Goal 1 to establish international food standards that address current and emerging food issues by promoting a harmonized approach to risk analysis.

- i. Goal 1, Objective 1.1: *Establish new and review existing Codex standards, based on priorities of the CAC- Activity 1.1.1*
- ii. Goal 1, Objective 1.2: *Proactively identify emerging issues and Member needs and, where appropriate, develop relevant food standards- Activity 1.2.2*

7. Information on the relation between the proposal and other existing Codex documents

The proposed work will be strongly linked to and guided by, but not limited to the:

- Working Principles for Risk Analysis for Application in the Framework of the Codex Alimentarius;
- Risk Analysis Principles Applied by the Codex Committee on Pesticide Residues
- Working Principles for Risk Analysis for Food Safety for Application by Governments

8. Identification of any requirement for and availability of expert scientific advice

Relevant scientific advice from JMPR specifically on gaps and uncertainties in the risk analysis of EDCs may be appropriate.

9. Identification of any need for technical input to the standard from external bodies so that this can be planned for the proposed timeline for completion of the new work

Not seen at this stage.

10. Proposed timeline for completion of work

Approval, in principle, of the work proposal by CCEXEC / CAC and establishment of the EWG	July 2018
Consideration of new work proposal by the relevant Codex Committee (the Codex Committee on Pesticides Residues)	April 2019
Adoption of the guidelines by CAC at Step 5	July 2020
Adoption of the guidelines by CAC at Step 8	July 2021