European Crop Protection

Regulating endocrine disruptors:

What are the key issues?

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The issue in a nutshell

When it comes to regulating hormone-active substances, finding the right balance is key. We need to protect human health and the environment, and it is right that endocrine disruptors, with the potential to do harm, are regulated in such a way to prevent that harm from occurring. But many products – just like coffee or soya – contain substances that are endocrine active, meaning they have a short-term, benign effect on hormones. Just like no-one would want to ban coffee, we shouldn't ban plant protection or biocidal products that are safe and bring important societal benefits. That is why the EU's criteria for endocrine disruptors must address the circumstances where those substances pose a real risk.

What is happening?

In recent years an increase in hormone-related diseases such as certain cancers, reproductive health disorders, diabetes and obesity has raised concerns and some have questioned whether chemicals may play a role. It is extremely difficult, today, to assess whether and to what extent everyday exposure to chemicals influences the prevalence or severity of these ddiseases, alongside established risk factors such as genetics, diet and lifestyle. Nevertheless, the regulatory authorities reacted to these concerns and included endocrine disrupting properties under the hazard-based cut-off criteria of the EU regulations that govern the sale of plant protection (1107/2009)[1] and biocidal (528/2012)[2] products.

Under the cut-off criteria, substances are authorised according to their intrinsic properties, regardless of the risk to human health and the environment under realistic conditions of exposure and use. If a substance satisfies these criteria, it is classed as hazardous and banned.

The European Commission is working on defining endocrine-disrupting properties. It published a first draft of the criteria options, which has not been implemented. Instead, the European Commission has undertaken a public consultation as part of its initial impact assessment in this legislative process. Once the criteria have been defined, substances considered to have endocrine-disrupting properties will not be authorised for use in the European Union.

What is the industry's position?

We, the European crop protection industry, are committed to the health and wellbeing of citizens and our natural environment. *After all, we, our families and our friends can be exposed to these products just like other European citizens!* It is our responsibility to ensure that our products are safe and that we provide clear information on any associated risks. This is why we believe that endocrine-disrupting chemicals must be properly regulated. We test new products extensively to ensure that they can be used safely and effectively. Together with independent authorities and institutions like the OECD, the industry actively contributes to the development of new and improved testing guidelines and methodologies that can detect endocrine-active and -disruptive effects.

The European Crop Protection Association[3] supports the adoption of criteria that identify the substances of real concern, namely those which present a demonstrable risk under realistic conditions of exposure. The criteria should be in line with the WHO definition[4] and be scientifically valid, unambiguous and practicable. This will allow the real risk of using a product to be taken into account. The criteria should also clearly distinguish between endocrine activity, which does not lead to irreversible negative consequences, and endocrine disruption, which does.

If the criteria for endocrine-disrupting chemicals are poorly defined there is a very real risk of a significant adverse impact on society. An overly-cautious approach will unintentionally remove products that not only do not cause adverse effects, but are beneficial to society, and this could have a negative impact on livelihoods, food prices, crop availability, the economy, innovation and trade.

It is therefore important to get the criteria for endocrine disruptors absolutely right. How the criteria are eventually set will have an impact in a range of areas, including public health, the environment, the economy and more. We welcome the public consultation and impact

[1] EC 1107/2009, Annex II, 3.6.5
[2] EU 528/2012, Article 5.1.d
[3] ECPA's position on the criteria for the determination of endocrine disrupting properties under Regulation 1107/2009
[4] The WHO defines an endocrine disruptor as "a substance or mixture that alters functions of the endocrine system and consequently causes adverse health effects in an intact organism or its progeny, or (sub) populations".

assessment to follow. We also welcome the European Commission's recommendations that risk assessment, socio-economic considerations and risk-benefit analysis be considered. However we believe that a complete risk assessment option should have been included in the the European Commission's proposed options for the criteria. In order to only capture the substances which are of regulatory concern and to avoid unwarranted concern, it is crucial that only one category be created for endocrine disruptors.

What are we calling for?

1. Scientific and realistic regulatory criteria to identify endocrine disruptors

Clear and scientifically-based criteria for endocrine disruptors will lead to higher confidence in the EU as an institution that takes societal concerns seriously, while enabling companies to make business decisions on a reliable basis.

2. The adoption of regulatory criteria that are scientifically valid, unambiguous and practicable, and take the actual risk into account

There should be consideration of the weight of evidence, the potency of the substance and whether exposure to the substance is likely to reach a level where it can cause adverse effects. If not, then there is no relevant health risk.

3. An objective and transparent discussion with all concerned

The topic is emotional and politically sensitive. This is why it is critical that an evaluation of the options for the criteria, in which all stakeholder concerns are addressed, be undertaken on a solid scientific basis.

4. A detailed consideration of unintended consequences

The over-regulation of endocrine disruptors would have far-reaching consequences for trade, innovation, competitiveness and food security.

What is the potential negative impact of the proposed criteria?

If the first draft of the criteria as put forward by the European Commission were implemented, significant negative impact in five key areas could arise.

Impact on agriculture and yields

The impact on European agricultural output would be substantial, and could be catastrophic. The yield impact on key crops such as wheat, potatoes, oilseed rape and vines are projected to be **10-20%** in an average year – with **losses of up to 50%** possible in years of high disease pressure.[1] The Irish Agriculture and Food Development Agency Teagasc estimates that the loss of triazoles would render succinate dehydrogenase inhibitor (SDHI) fungicides useless due to crop resistance, and would probably lead to the **complete collapse of the Irish wheat industry,** because it would no longer be economically viable.[2] A similar picture of agricultural collapse across the continent is described by others, including as much as **95% of Spanish grain** cultivation being threatened, and **95% of Spain's olive cultivation** threatened by the glyphode moth.[3]

Impact on the economy

Massive food inflation would not be the only negative impact on the European economy. One study estimates that lost wheat crops alone would **take €4.6bn out of the European economy by 2020**.[4] Moreover, as Europe would no longer be able to fully meet its own wheat consumption requirements, this would **push up imports and negatively distort Europe's trade balance sheet.**

Impact on innovation

The proposed criteria options will also adversely affect innovation. On average, each new active substance requires **10 years of research and development** and an investment of some **€200m**.[5] Companies could not justify such investments if new solutions risk being banned under the proposed criteria, even if completely safe for use in realistic situations. This will see **innovation flow out of Europe,** with further negative consequences on the European economy.

[1] PSD/CRD Evaluation (2009). Proposal for a regulation of the European Parliament and of the Council concerning the placing of plant protection products on the market
[2] Spink, J & Kildea, S. Overview of the potential impact the withdrawal of azoles as a result of an inappropriate endocrine disruption definition may have upon wheat disease control programmes and production in Ireland. Teagasc Oak Park, Carlow, Ireland
[3] Asociacion Empresarial para la Proteccion de las Plantas (AEPLA) (2014). Estudio de impacto AEPLA alteradores endocrinos
[4] Nomisma (2012). The Assessment of the Economic Importance of Azoles in European Agriculture: Wheat Case Study
[5] Phillips McDougall. (2012) R&D trends for chemical crop protection products and the position of the European Market

Impact on crop protection product availability

The endocrine-disruption criteria proposed are expected to **severely reduce the availability of crop protection products** in Europe, with a substantially greater impact than originally expected when Regulation 1107/2009 was adopted. Based on a 2009 UK government assessment of active substances, some **35-45%** of the crop protection products currently available to European farmers could be removed from the market. Fungicides in particular are most vulnerable. Applying the UK criteria, approximately **80% of fungicide products** currently used across the EU would be removed: in Germany, **10** of the most important cereal fungicide products would not be available; in France, **7** of the top ten most-relied-upon products would be lost to farmers.[6]

Impact on consumer food prices

Vastly reduced crop yields will inevitably push **consumer food prices through the roof**, which would be detrimental to European consumers' purchasing power and ability to affordably feed their families. For example, Teagasc estimates that **price increases of up to 66% would be necessary** to adequately compensate farmers for yield losses.[7]

Impact on trade

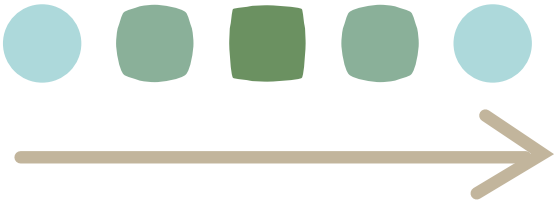
There are serious concerns that the proposed criteria could have a **far-reaching negative impact on global commerce**, not least as purely hazard-based criteria are inconsistent with the WTO's SPS Agreement (Agreement on the Application of Sanitary and Phytosanitary Measures).[8] Imposing these criteria on non-EU producers could potentially cause **damaging trade wars.**

[6] ECPA (2014). ECPA's position on the criteria for the determination of endocrine disrupting properties under Regulation 1107/2009
[7] Spink, J & Kildea, S. Overview of the potential impact the withdrawal of azoles as a result of an inappropriate endocrine disruption definition may have upon wheat disease control programmes and production in Ireland. Teagasc Oak Park, Carlow, Ireland
[8] WTO Agreement on Sanitary and Phytosanitary Measures

The endocrine system, endocrine activity, and endocrine disruption

The endocrine system includes a complex set of glands which release hormones (chemical messengers) into the body to control the regulation of important processes such as growth, development, onset of puberty and behaviour.

Many substances, natural and synthetic, can interact with the endocrine system without adverse effect. This is called endocrine *activity*. An endocrine-active substance has a temporary and benign effect on the endocrine system. The endocrine system returns to normal.



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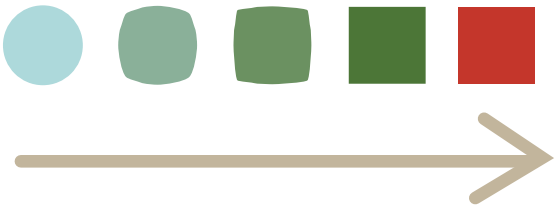
Naturally-occurring endocrine-active substances (EASs) occur in everyday products such as rice, coffee, soya beans or paracetamol, a common painkiller. The endocrine system is naturally dynamic and can quickly adjust to exposure to endocrine-active substances. Some crop protection products are endocrine active, too. However, human exposure to the endocrine-active compounds in these products is orders of magnitude lower than exposure to common EASs such as caffeine, sugar and phytoestrogens in foods like soya protein.

Endocrine *disruption* occurs when substances have an adverse effect by altering the functioning of the endocrine system, causing irreversible change and/or illness. In other words, an endocrine disruptor interferes with the endocrine system to cause a harmful effect.



An endocrine disruptor interferes with the endocrine system to cause a harmful effect.

The idea of endocrine disruption is not new, and active substances used in plant protection and biocidal products in the EU undergo comprehensive testing, including for endocrine-related adverse effects. Substances are approved only if deemed safe by EU authorities. Furthermore, re-registration of substances is required every ten years, ensuring that only substances which have been examined according to the latest requirements are allowed.

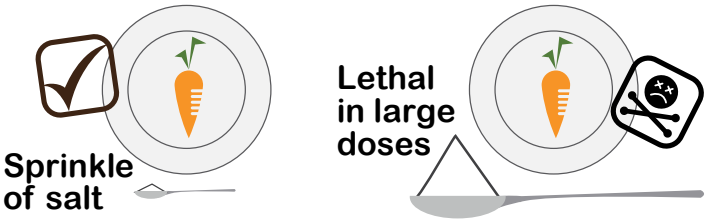
Substances which do not cause an adverse effect under realistic conditions of use should not be considered endocrine disruptors.

The importance of dosage...

Of key importance in evaluating endocrine disruption are issues of substance *dosage* and *potency*.

The father of toxicology, Paracelsus, established the now well-known principle that "the dose makes the poison": a product or substance only produces a harmful effect when its dose exceeds a living being's ability to cope with it. A larger *dose* of some substances can have an adverse effect whereas a smaller dose of the same substance does not: it is the amount that matters.

Salt provides a good example of this: not only does salt add flavour to our food, humans actually require salt in small doses to survive. However consumed in large doses, salt is poisonous, can cause illnesses and is potentially fatal – 57g is considered a fatal dose for a child.



Humans need a small amount of salt in their diet. Without it they would die. However salt can be lethal if too much is consumed.

The tiny amount of formaldehyde naturally present in pears doesn't mean pears aren't safe to eat. Drinking a litre of formaldehyde however isn't a good idea.

Another good example is provided by pears. No-one would advise you not to eat pears for health reasons. Yet pears contain trace amounts of formaldehyde. In the concentrations present in pears, it poses absolutely no risk to human health. On the other hand, ingestion of 30ml of formaldehyde with a concentration of 37% has been reported to cause death.[1] So while no-one would suggest you should drink formaldehyde, this doesn't mean that pears aren't safe to eat.

Even vitamins offer a good example of the importance of dosage. A lack of vitamin C is known to cause scurvy, whereas too much of it can lead to a series of negative side effects. Ergo, there is a range in which vitamins enable a normal healthy life. With vitamins especially there are times in our life when it is critical to define this dose range correctly and to get the dosage right: for example, vitamin D supplements are recommended for growing children to ensure the healthy development of growing bones.

If the same substance is used at doses that do not cause an adverse effect, it is safe for use and should not be considered an endocrine disruptor. As the President of the German Federal Institute for Risk Analysis Professor Andreas Hensel puts it, "in contrast to what people might think, the simple presence of a particular substance is not reason in itself for concern. A substance will only ever have an effect if it is present in a certain concentration."[2]

Only those substances applied at a dosage that leads to an adverse effect should be considered an endocrine disruptor.

[1] Medical Management Guidelines for Formaldehyde
[2] Hensel, Andreas (2011). Lebensmittelsicherheit zwischen Weltanschauung und globalisiertem Handel. Presentation given at the German Federation for Food Law and Food Science.

...and potency

The *potency* of a substance is an essential part of regulatory safety evaluation and is an important factor when establishing safe doses. Potency is a measure of a substance's strength: at similar dosages, a highly-potent substance produces a greater effect whereas a substance of low potency will produce little or no effect. But even the use of higher-potency substances can be safe if exposure levels are low: again it is the amount that matters.

While a sports car and a bicycle will both get you from A to B, a sports car is far more potent than a bicycle.

A good way to illustrate potency is to compare two modes of ground transport. Take for example a bicycle and a sports car. Both work on the same pathway (ground). Both will get you from A to B. But while they are both methods of ground transportation that ultimately do the same job, a sports car is far more powerful – and therefore has a much stronger impact (potency) – than a bicycle.

Dosage and potency are closely linked, and both must be taken into consideration when evaluating the effects of substances on the endocrine system.

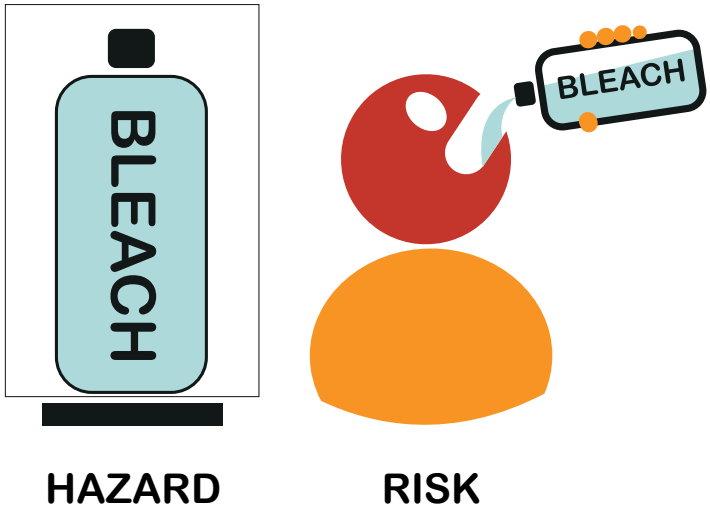
Risk & hazard

One of the areas of most confusion is the difference between a 'risk' and a 'hazard'. Sometimes they are, mistakenly, used interchangeably. But 'risk' and 'hazard' are fundamentally different.

Anything that can cause harm represents a hazard, whereas risk describes the chance of harm being done – in terms of both the likelihood of harm, and the extent of that harm.

A good way of illustrating the difference is to take as an example a bottle of bleach, a common household substance many of us have at home. It has many practical household uses, and in everyday usage does not cause any harm to human health. Sitting in your kitchen cupboard, a bottle of bleach can be said to represent a hazard: it bears the potential to cause harm due to its intrinsic properties — but in reality it doesn't because no one is exposed to it. If you use it responsibly for household chores, the risk is negligible. If, however you were to ingest bleach, this would present a severe risk. Bleach used responsibly does not cause any harm. Drinking it does.

Similarly, a shark seen from the safety of the shore represents a hazard, and it becomes a risk only when you enter the water. It is not that the shark's teeth become sharper as soon as you leave the shore – the properties of the shark remain the same – it is the fact that you are now in reach of those teeth that puts you in danger.



A bottle of bleach sitting in the cupboard of your kitchen doesn't represent a risk to your health. Drinking it does.

Risk assessment examines the intrinsic properties of a substance and the hazard which could derive from it and determines if this substance is detrimental to human health or the environment in real-life conditions of exposure.

Hazard assessment on the other hand takes into account only the intrinsic properties of a substance without considering its real-life usage.

A truly scientific approach to regulating endocrine disruptors must use a real-life risk-based evaluation, rather than considering only the intrinsic properties of substances. This means applying the full risk assessment process in EU legislation, which takes into account all the available information of good quality on both the hazard and real-life exposure. No one single study will be sufficient to reach regulatory decisions in substances because of the need to provide data on the adverse effect and mode of action.

Key issues for the agri-food value chain

(1/2)

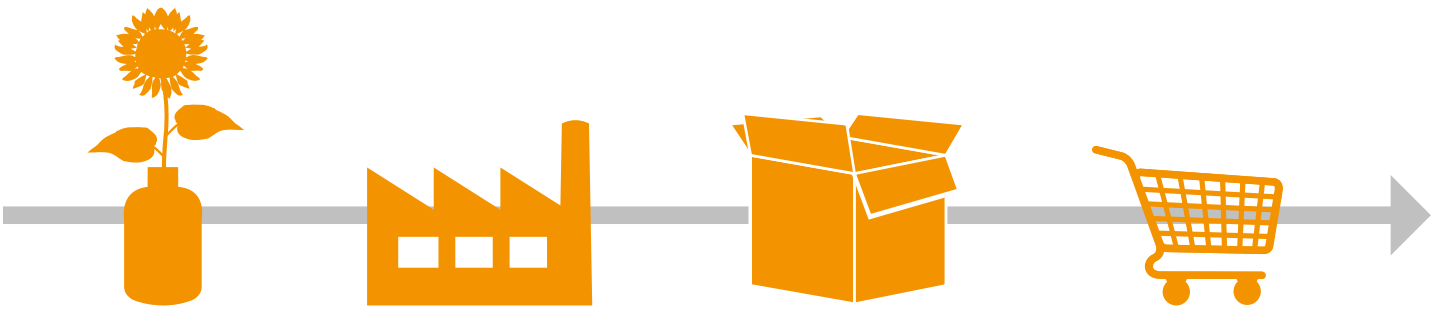
In recent years an increase in hormone-related health disorders such as certain cancers, reproductive deficits, diabetes and obesity has raised concerns and some have questioned whether chemicals may play a role.. It is extremely difficult, today, to assess whether and to what extent everyday exposure to chemicals influences the prevalence or severity of these diseases, alongside established risk factors such as genetics, diet and lifestyle. Nevertheless, the regulatory authorities reacted to these concerns and included endocrine disrupting properties under the hazard-based cut-off criteria of the EU's plant protection and biocidal product regulations.[1] If a substance satisfies these criteria it is classed as hazardous and banned. The European Commission is working on defining the criteria that would establish which substances are, in fact, endocrine disruptors.

When it comes to regulating hormone-active substances, finding the right balance is key. We need to protect human health and the environment, and it is right that endocrine disruptors, with the potential to do harm, are regulated in such a way to prevent that harm from occurring. But many products — just like coffee and soya — contain substances that are endocrine active, meaning they have a short-term, benign effect on hormones. Just like no-one would want to ban coffee, we shouldn't ban crop protection and biocidal products that are safe and bring important societal benefits. That is why the EU's criteria for endocrine disruptors must address the circumstances where those substances pose a real risk.

We, the European crop protection industry, believe that a complete risk assessment option should be included in the proposed option for the criteria put forward by the European Commission. Already today, we test new products extensively to ensure that they can be used safely and effectively. This includes numerous studies that detect both endocrine-active and -disruptive effects. Together with independent authorities and institutions like the OECD, the industry actively contributes to the development of new and improved testing guidelines and methodologies.

We support the adoption of criteria that identify the substances of real concern, namely those which present a demonstrable risk under realistic conditions of exposure. The criteria should be in line with the WHO definition[2] and be scientifically valid, unambiguous and practicable.

If the criteria for endocrine-disrupting chemicals are poorly defined, the impact on useful and safe products would put the agri-food value chain at a disadvantage without bringing an improvement to human or environmental health.



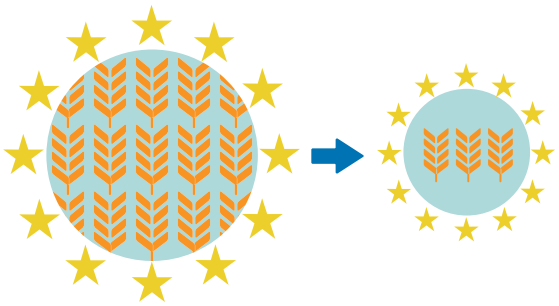
[1] EC 1107/2009, Annex II, 3.6.5
[2] The WHO defines an endocrine disruptor as "a substance or mixture that alters functions of the endocrine system and consequently causes adverse health effects in an intact organism or its progeny, or (sub) populations".

Key issues for the agri-food value chain

(2/2)

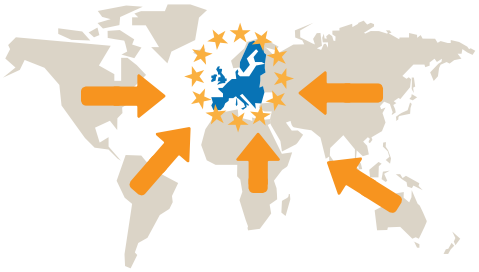
What is the potential impact on the European agri-food value chain?

• *Increased risk of resistance:* Unnecessarily removing effective actives may remove classes of chemistry and reduce the options for rotation of products to avoid resistance; less effective alternatives may need to be applied more frequently, also tending to increase the risk of resistance and increasing inputs (labour costs), thereby increasing commodity prices.



Due to loss of tools, farmers could experience a decrease in yields of up to 50%, thereby limiting commodity availability.

• *Reduced availability of raw materials:* Endocrine-disruptor regulation in the EU is likely to affect imports. If maximum residue levels are set at the default level (0.01 mg/kg body weight), commodities which have been treated with a banned substance can no longer be imported into the EU.



-60% The EU agri-food value chain could see commodity imports to the EU drop by 60% thereby limiting availability.

- *Lower-quality commodities:* Currently most at risk by the endocrine-disruptor cut-off in Europe are the azole fungicides, which combat natural toxins such as mycotoxins in cereal. Mycotoxin contamination significantly lowers the value and quality of the crop, in turn impacting the value of the final product.
- *Unwarranted concerns:* Introducing categories of endocrine disruptors as being considered by the European Commission will certainly capture more pesticides than a single category of substances shown to be endocrine disruptors. While substances in the "suspected" or "possible" categories may remain available from a regulatory perspective because they meet all existing safety requirements, the simple fact that they are in a category could raise unwarranted concerns.

What can you do to ensure that the agri-food value chain can still benefit from European agriculture and innovation?

It is important for affected parties to voice their opinion and to actively participate in the public debate around the issue of endocrine disruptors.

The Commission must be made aware of the implications of choosing an option which does not include risk assessment. Risk assessment is in line with the WTO SPS Agreement (Agreement on the Application of Sanitary and Phytosanitary Measures). To ensure that the agri-food value chain has continuous access to high-quality raw materials without lowering standards of protection for human health or the environment, all available data must be taken into account; a weight-of-evidence approach should be applied; elements such as potency should be included, and there should be proof of a robust causal relationship between the endocrine mode of action and an adverse effect. In order to only capture the substances which are of regulatory concern and to avoid unwarranted concerns, it is crucial that only one category be created for endocrine disruptors.

Key issues for the biocides value chain

(1/2)

In recent years an increase in hormone-related health disorders such as certain cancers, reproductive deficits, diabetes and obesity has raised concerns and some have questioned whether chemicals may play a role. It is extremely difficult, today, to assess whether and to what extent everyday exposure to chemicals influences the prevalence or severity of these diseases, alongside established risk factors such as genetics, diet and lifestyle. Nevertheless, the regulatory authorities reacted to these concerns and included endocrine disrupting properties under the hazard-based cut-off criteria of the EU's biocidal products regulation.[1] The European Commission is working on defining the criteria that would establish which substances are, in fact, endocrine disruptors.

When it comes to regulating hormone-active substances, finding the right balance is key. We need to protect human health, and it is right that endocrine disruptors, with the potential to harm human health, are regulated in such a way to prevent that harm from occurring. But many products — just like coffee and soya — contain substances that are endocrine active, meaning they have a short-term, benign effect on hormones. Just like no-one would want to ban coffee, we shouldn't ban crop protection and biocidal products that are safe and bring important societal benefits. That is why the criteria must address the circumstances where those substances pose a real risk.

We believe that a complete risk assessment option should be included in the proposed options for the criteria put forward by the European Commission. Already today, we test new products extensively to ensure that they can be used safely and effectively. This includes numerous studies that detect both endocrine-active and -disruptive effects. Together with independent authorities and institutions like the OECD, the industry actively contributes to the development of new and improved testing guidelines and methodologies.

We support the adoption of criteria that identify the substances of real concern, namely those which present a demonstrable risk under realistic conditions of exposure. The criteria should be in line with the WHO definition[2] and be scientifically valid, unambiguous and practicable.

If the criteria for endocrine-disrupting chemicals are poorly defined, the impact on useful and safe products would put the biocides value chain at a disadvantage without bringing an improvement to human or environmental health.

This realisation has already resulted in the inclusion of an additional derogation, which recognises that a hazardous substance may be permitted for biocidal use if the socio-economic benefits outweigh the risks. However, this derogation does not apply for products that are made available to the general public. In any event, we believe that regulation by derogation is poor regulation.

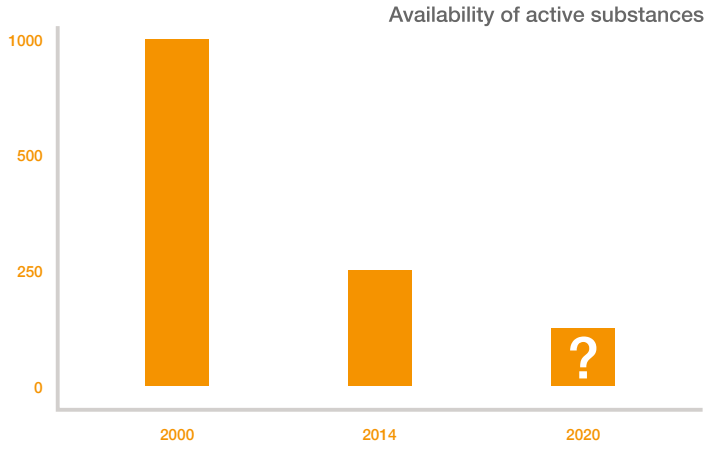
[1] EU 528/2012, Article 5.1.d
[2] The WHO defines an endocrine disruptor as "a substance or mixture that alters functions of the endocrine system and consequently causes adverse health effects in an intact organism".

An update for the biocides value chain

(2/2)

What is the potential impact on the biocides value chain?

• *Loss of consumer products:* Given the lack of derogations for consumer products specifically, these are most at risk. If the active substances or any of the co-formulants in the product meet the criteria for endocrine disruptors, these products will be banned for consumer use, without any consideration regarding the essentiality or benefits they can bring to the consumer. This in turn would mean a loss of income for retailers and producers (and increase the occurrence of bugs in homes).



There has already been a massive drop in the number of active substances available on the market in recent years.

• *Another hit on the toolbox:* The Biocidal Products Regulation has seen fewer than ten new active substances arrive on the market since 2000. Coupled with a 75% loss in active substances since the inception of the EU biocides regulatory process (1000 actives in the year 2000, 250 actives in the year 2014), further loss of actives will simply increase the risk of resistance developing to the few that are left. Consequently this can lead to the increase of infectious diseases (such as ones that are mosquito-borne) with increased risks of epidemics (eg if anti-microbial products are less effective).

• *Greater delay in the evaluation process:* Not only those products which are currently on the market, but also those in the pipeline will be affected by the ever-greater burden placed on regulators. The biocides industry is already anticipating a 14-year delay on a 10-year programme, which is hard to reconcile with a pressing need to assure human health and environmental safety.

What can you do to ensure that the biocides value chain can still benefit from a high number of innovative products?

It is important for affected parties to voice their opinion and to actively participate in the public debate around the issue of endocrine disruptors.

The Commission must be made aware of the implications of choosing an option which does not include risk assessment. To ensure that the biocides value chain does not experience a further loss of products without lowering standards of protection for human health or the environment, all available data must be taken into account; a weight-of-evidence approach should be applied; elements such as potency should be included, and there should be proof of a robust causal relationship between the endocrine mode of action and an adverse effect. In order to only capture the substances which are of regulatory concern and to avoid blacklisting, it is crucial that only one category be created for endocrine disruptors.

Key issues for agriculture
(1/2)

In recent years an increase in hormone-related health disorders such as certain cancers, reproductive deficits, diabetes and obesity has raised concerns and some have questioned whether chemicals may play a role. It is extremely difficult, today, to assess whether and to what extent everyday exposure to chemicals influences the prevalence or severity of these diseases, alongside established risk factors such as genetics, diet and lifestyle. Nevertheless, the regulatory authorities reacted to these concerns and included endocrine disruptors under the hazard-based cut-off criteria of the EU's plant protection products regulation.[1] The European Commission is working on defining the criteria that would establish which substances are, in fact, endocrine disruptors.

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Key issues for agriculture

(2/2)

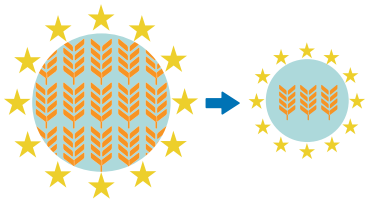
What is the potential impact on European farmers?

• *Farmers will lose necessary pesticide products:* Based on data from a 2009 study by the UK Chemicals Regulation Directorate, the European Crop Protection Association estimates that up to 37 active substances will be eliminated should the definition for endocrine disruptors not include risk assessment. This would mean that 35-45% of all pesticide products would no longer be available in Europe.[1] The loss of a high number of pesticide products means there will be fewer solutions at hand to combat pests, leading to greater pest pressure. In extreme cases this could lead to the total collapse of entire agricultural sectors of activity. For example, the Irish Agriculture and Food Development Authority Teagasc predicts that this can lead to entire crops such as winter wheat becoming economically unviable to grow in Ireland.

In France 7 of the top 10 fungicide products for cereals would no longer be available according to data by the Chemical Regulation Directorate (CRD)

• *Negative impact on income:* With more pests comes lower yield. In addition, since many of the substances identified are fungicides, mycotoxins will likely lead to lower-quality crops. This will have a direct impact on the value of the crops, and therefore on farmers' incomes.

• *Unwarranted concerns:* Introducing categories of endocrine disruptors as being considered by the European Commission will certainly capture more pesticides than a single category of substances shown to be endocrine disruptors. While substances in the "suspected" or "possible" categories may remain available from a regulatory perspective because they meet all existing safety requirements, the simple fact that they are in a category could raise unwarranted concerns.



Due to loss of tools, farmers could experience a decrease in yields of up to 50%, thereby limiting commodity availability.

What can you do to ensure that farmers can still benefit from a high number of innovative pesticide products?

It is important for affected parties to voice their opinion and to actively participate in the public debate around the issue of endocrine disruptors.

The Commission must be made aware of the implications of choosing an option which does not include risk assessment. To ensure that European farmers have access to all necessary solutions without lowering standards of protection for human health or the environment, all available data must be taken into account; a weight-of-evidence approach should be applied; elements such as potency should be included, and there should be proof of a robust causal relationship between the endocrine mode of action and an adverse effect. In order to only capture the substances which are of regulatory concern and to avoid unwarranted concerns, it is crucial that only one category be created for endocrine disruptors.

[1] PSD/CRD Evaluation (2009). Proposal for a regulation of the European Parliament and of the Council concerning the placing of plant protection products on the market

Key issues for policy makers

(1/2)

In recent years an increase in hormone-related health disorders such as certain cancers, reproductive deficits, diabetes and obesity has raised and some have questioned whether chemicals may play a role. It is extremely difficult, today, to assess whether and to what extent everyday exposure to chemicals influences the prevalence or severity of these diseases, alongside established risk factors such as genetics, diet and lifestyle. Nevertheless, the regulatory authorities reacted to these concerns and included endocrine disrupting properties under the hazard-based cut-off criteria of the EU's plant protection and biocidal product regulations.[1] The European Commission is working on defining the criteria that would establish which substances are, in fact, endocrine disruptors.

When it comes to regulating hormone-active substances, finding the right balance is key. We need to protect human health and the environment, and it is right that endocrine disruptors, with the potential to do harm, are regulated in such a way to prevent that harm from occurring. But many products — just like coffee and soya — contain substances that are endocrine active, meaning they have a short-term, benign effect on hormones. Just like no-one would want to ban coffee, we shouldn't ban crop protection and biocidal products that are safe and bring important societal benefits. That is why the EU's criteria for endocrine disruptors must address the circumstances where those substances pose a real risk.

We, the European crop protection industry, believe that a complete risk assessment option should be included in the proposed options for the criteria put forward by the European Commission. Already today, we test new products extensively to ensure that they can be used safely and effectively. This includes numerous studies that detect both endocrine- active and -disruptive effects. Together with independent authorities and institutions like the OECD, the industry actively contributes to the development of new and improved testing guidelines and methodologies.

We support the adoption of criteria that identify the substances of real concern, namely those which present a demonstrable risk under realistic conditions of exposure. The criteria should be in line with the WHO definition[2] and be scientifically valid, unambiguous and practicable.

If the criteria for endocrine-disrupting chemicals are poorly defined, the impact on useful and safe products would put European agriculture at a disadvantage without bringing an improvement to human or environmental health.

In their Roadmap for endocrine disruption, the Commission suggests that amendments could be made to the Plant Protection Products Regulation which would allow for consideration of risk assessment elements and also consideration of socio-economic risk-benefit to avoid a total ban if an active was identified as an endocrine disruptor. However, these changes would require a separate legislative procedure with no guarantee of success. Therefore, the criteria should be decided without assuming that these derogations will be applicable.

[1] EC 1107/2009, Annex II, 3.6.5

[2] The WHO defines an endocrine disruptor as "a substance or mixture that alters functions of the endocrine system and consequently causes adverse health effects in an intact organism or its progeny, or (sub) populations".

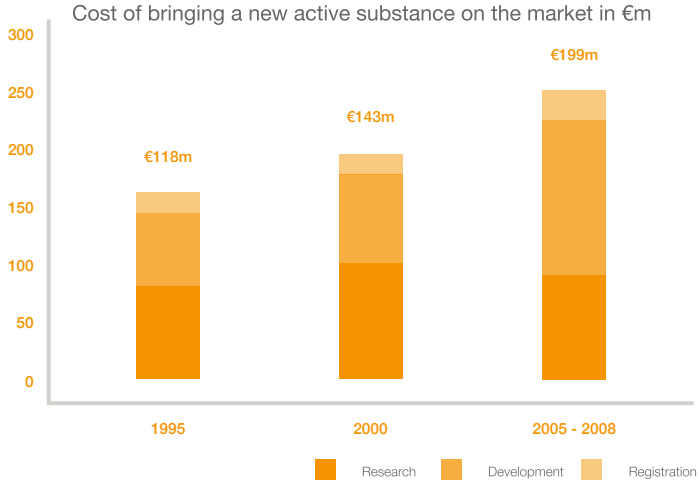
Key issues for policy makers

(2/2)

What is the potential impact on Europe, its Member States and its citizens?

In France 7 of the top 10 fungicide products for cereals would no longer be available according to data by the Chemical Regulation Directorate (CRD)

• *Farmers will lose necessary tools:* Every harvest is threatened by different pests, such as weeds or insects. In order for farmers to be able to avoid resistance, rotation of treatment types is necessary. For this, availability and access to different modes of action in pesticide products is crucial. But based on data from a 2009 study by the UK Chemicals Regulation Directorate, the European Crop Protection Association estimates that up to 37 active substances will be eliminated should the definition for endocrine disruptors not include risk assessment. This would mean that 35-45% of all pesticide products would no longer be available in Europe.[3]



The increasing cost of bringing a new Active Ingredient to the market according to a study undertaken for the European Crop Protection Association and CropLife America

• *Loss of competitiveness:* Following the loss of a high number of pesticide products, greater pest pressure will eat away at farmers' output and earnings. This will in turn have a negative effect on jobs in the agriculture value chain, and has already led to a decline in investment in the crop protection industry in Europe. Should the European Commission chose to set an MRL of 0.01mg/kg for substance with endocrine disrupting properties, a loss of imports of commodities treated with banned substances could lead to a loss of competitiveness in the European food value chain.

• *Flight of innovation:* Due to a regulatory environment which is increasingly driven by a precautionary approach, R&D investments lead to a smaller number of new crop protection products being developed for the European market: from 33.3% in the 1980s to 25% in the 1990s to just 7.7% in the 2005-14 period.[4] Overly-precautious criteria to determine endocrine disruptors will further discourage investment in innovation in Europe.

What can you do to ensure that we can still benefit from European agriculture and innovation?

The Commission should be made aware of the implications of choosing an option which does not include risk assessment. The issue should thus be addressed with the relevant European Commission services.[5]

Furthermore, it is important to input into the process of defining criteria for endocrine disruptors at an early stage – especially with the 'Lisbonisation' of the Plant Protection Regulation (1107/2009) – where a delegated act could be adopted without the need for a vote by Member-States representatives in the Standing Committee on Plants, Animals, Food and Feed.

[3] PSD/CRD Evaluation (2009). Proposal for a regulation of the European Parliament and of the Council concerning the placing of plant protection products on the market
[4] Phillips McDougall. (2012) R&D trends for chemical crop protection products and the position of the European Market
[5] DG Health, DG Environment, Secretariat General, DG Agriculture, DG Research and Development, DG Trade

Key issues for EU trading partners

(1/2)

In recent years an increase in hormone-related health disorders such as certain cancers, reproductive deficits, diabetes and obesity has raised concerns and some have questioned whether chemicals may play a role. It is extremely difficult, today, to assess whether and to what extent everyday exposure to chemicals influences the prevalence or severity of these diseases, alongside established risk factors such as genetics, diet and lifestyle. Nevertheless, the regulatory authorities reacted to these concerns and included endocrine disrupting properties under the hazard-based cut-off criteria of the EU's plant protection regulation.[1] The European Commission is working on defining the criteria that would establish which substances are, in fact, endocrine disruptors.

Under the MRL legislation[2], the European Commission has the right to set a maximum residue level higher than 0.01mg/kg for substances which have been banned under EU regulation, which is a common practice and has so far limited the impact of other cut-off criteria on trade. However, there is a possibility that for substances with endocrine disrupting properties, the Commission will set the MRL at 0.01mg/kg, effectively banning the import of commodities treated with substances identified as endocrine disruptors.

When it comes to regulating hormone-active substances, finding the right balance is key. We need to protect human health and the environment, and it is right that endocrine disruptors, with the potential to do harm, are regulated in such a way to prevent that harm from occurring. But many products — just like coffee and soya — contain substances that are endocrine active, meaning they have a short-term, benign effect on hormones. Just like no-one would want to ban coffee, we shouldn't ban crop protection and biocidal products that are safe and bring important societal benefits. That is why the EU's criteria for endocrine disruptors must address the circumstances where those substances pose a real risk.

We, the European crop protection industry, believe that a complete risk assessment option should be included in the proposed options for the criteria put forward by the European Commission. Already today, we test new products extensively to ensure that they can be used safely and effectively. This includes numerous studies that detect both endocrine-active and -disruptive effects. Together with independent authorities and institutions like the OECD, the industry actively contributes to the development of new and improved testing guidelines and methodologies.

We support the adoption of criteria that identify the substances of real concern, namely those which present a demonstrable risk under realistic conditions of exposure. The criteria should be in line with the WHO definition[3] and be scientifically valid, unambiguous and practicable.

Poorly defining the criteria for endocrine-disrupting chemicals could severely impact international trade without bringing an improvement to human or environmental health.

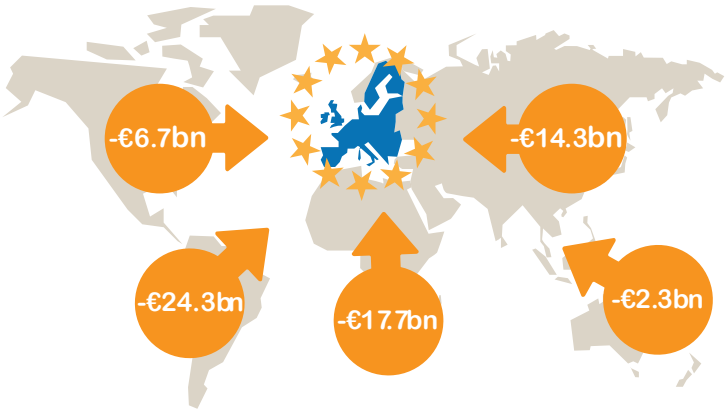
[1] EC 1107/2009, Annex II, 3.6.5
[2] EC 396/2005
[3] The WHO defines an endocrine disruptor as "a substance or mixture that alters functions of the endocrine system and consequently causes adverse health effects in an intact organism or its progeny, or (sub) populations".

Key issues for EU trading partners

(2/2)

What is the potential impact for the trading partners of the European Union?

Negative effects on trade: Due to the high likelihood of very strict MRLs (0.01mg/kg) for substances banned under the endocrine-disruptor cut-off, trade barriers unfavourable to exporting third countries will be set up for treated commodities. Trade disruption could also lead to a wide variety of knock-on effects, such as trade diversion to other countries with less purchasing power, or stockpiling of commodities. Globally, exports to the EU could collapse by up to €65.4bn.[1]



-€65.4bn World commodity producers could see EU export values drop by up to €65.4bn, which will have a significant impact on every global region.

What can you do to ensure that international trade is not disrupted?

It is important for affected parties to voice their opinion and input into the process of defining criteria for endocrine disruptors. The most practical way to raise concerns with the European Commission is to participate in the public consultation, which has been set up exactly for this purpose.

The example set by a hazard-based approach to endocrine disruptor legislation in the EU will risk being copied across other jurisdictions around the world.

Proportionate and science-based regulatory approach

Risk assessment should form the basis for regulating chemicals, including pesticides and biocides, because, unlike hazard-based assessment, it takes into account the huge amount of information available on the substances, as well as important factors such as exposure, in establishing safety standards.

The Commission must be made aware of the implications of choosing an option which does not include risk assessment. Risk assessment is the only option which is in line with the WTO SPS Agreement (Agreement on the Application of Sanitary and Phytosanitary Measures). To ensure that trade is not disrupted, all available data must be taken into account; a weight-of-evidence approach should be applied; elements such as potency should be included, and there should be proof of a robust causal relationship between the endocrine mode of action and an adverse effect. In order to only capture the substances which are of regulatory concern and to avoid blacklisting, it is crucial that only one category be created for endocrine disruptors.

[1] Brenner, K. (2013). Potential Trade Effects on World Agricultural Exporters of European Union Regulations on Endocrine Disruptors DTB Associates LLP.

Why is this news? Why is the issue of endocrine disruption so topical and why does the EU feel it needs to regulate in this area?

The idea of endocrine disruption is not new. However, in recent years an increase in hormone-related diseases such as certain cancers, reproductive health disorders, diabetes and obesity has raised concerns and some have questioned whether chemicals may play a role. The regulatory authorities reacted to these concerns and included endocrine disruptors under the hazard-based cut-off criteria of the EU's plant protection regulation.[1] The term "endocrine-disrupting properties" is included in EU regulations that govern the sale of plant protection (1107/2009) and biocidal (528/2012) products, but this term has not yet been defined.

According to current regulations, the EU was required to establish the criteria to define endocrine-disrupting properties by 14 December 2014. The European Commission has published a roadmap[2] with its proposed options for the criteria, and has completed a public consultation as part of its impact assessment in this legislative process. Once the final criteria are agreed, substances considered to have endocrine-disrupting properties will not be authorised for use in the European Union.

What is the endocrine system?

The endocrine system is a complex set of glands which release hormones (chemical messengers) into the body that control the regulation of important processes such as growth, development, puberty onset and behaviour. The endocrine system is naturally dynamic and responds to maintain bodily processes.

What is an endocrine disruptor?

Endocrine disruption occurs when substances have an adverse effect by altering the functioning of the endocrine system, causing irreversible change and/or illness. In other words, an endocrine disruptor interferes with the endocrine system to cause a harmful effect. WHO-IPCS has defined an endocrine disruptor as "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".

What is an adverse effect?

According to the WHO definition, an adverse effect represents "a change in morphology, physiology, growth, reproduction, 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."[3] This means an adverse effect is a reduction of the body's capability to function correctly.

Do endocrine disruptors lead to an increased rate of diseases in humans?

A report[4] by the WHO/UNEP claims that many endocrine-related diseases, such as cancers, reduced sperm count, obesity and diabetes are on the rise. While apparent correlation has been noted in some studies, other studies indicate no such correlation and overall no direct causal link has been established. There are often inferences that endocrine disrupting chemicals play a role, for example authors often state that they "refuse to rule out the

[1] EC 1107/2009, Annex II, 3.6.5
[2] Defining criteria for identifying Endocrine Disruptors in the context of the implementation of the Plant Protection Product Regulation and Biocidal Products Regulation
[3] World Health Organisation International Programme on Chemical Safety
[4] State of the Science of Endocrine Disrupting Chemicals p. viii

possibility" that an effect was caused by endocrine disruption. There is therefore a common understanding that endocrine disruption could contribute to increased rates of human disease without a clear demonstration that exposure to particular chemicals cause that disruption.

The chemical reality is that many of the claims about chemicals being 'linked' to diseases simply tell us that a chemical was present when an effect occurred, rather than showing that the chemical causes the effect. Caution is needed in reporting apparent correlations: it is in the nature of scientific experiments that many disappear when a further test is done or they turn out to be explained in other ways. If one were to plot the increase in the number of individuals diagnosed with autism during the period 1997 - 2007, and the increase in sales of organic food, the graph would show a direct correlation – but no one is suggesting eating organic food causes autism.

People should be protected against potentially harmful substances, and in the protection of human health it is critical the possibility to cause endocrine disruption be prevented. The overall current weight of scientific evidence does not support the view that pesticides are associated with the human diseases mentioned. In fact the one most consistent finding in almost all well conducted epidemiological studies on agricultural communities, is that farmers are healthier than the general population.

Are all pesticides endocrine disruptors?

No. Active substances used in plant protection and biocidal products in the EU undergo comprehensive testing, including for endocrine-related adverse effects. People should be protected against potentially harmful substances. That is why each crop protection product on the market is regulated and has been rigorously evaluated.

Substances are approved only if deemed safe by EU authorities. Furthermore, re-registration of substances is required every ten years, ensuring that only substances which have been examined according to the latest requirements are allowed.

Not every substance which interacts with the endocrine system is necessarily an endocrine *disruptor*. Many substances, natural and synthetic, interact with the endocrine system without adverse effect. This is called endocrine *activity*. An endocrine-active substance has a temporary and benign or insignificant effect on the endocrine system. The endocrine system returns to normal.

Are synthetic chemicals more likely to be endocrine disruptors?

No. All substances have the potential to be harmful irrespective of whether they are manufactured, copied from nature, or extracted directly from nature. In terms of chemical safety, 'industrial', 'synthetic', 'artificial' and 'man-made' do not necessarily mean 'damaging', and 'natural' does not necessarily mean 'safe' or 'better'.

Naturally-occurring endocrine-active substances (EASs) occur in everyday foods such as rice, coffee, carrots and soya beans. The endocrine system is naturally dynamic and can quickly adjust to exposure to endocrine-active substances. Like coffee, soya or paracetamol, a common painkiller, some crop protection products are endocrine active. Human exposure to crop protection products is orders of magnitude lower than exposure to common EASs such as caffeine, sugar and phytoestrogens in foods like soya protein.

Would organic farming be an alternative to using crop protection substances with endocrine disrupting properties?

Organic farmers use a number of natural chemicals to control pests, such as copper sulfate, which has been identified as a potential endocrine disruptor by the TEDX list[4]. Furthermore, organic farming cannot provide all of the solutions for a massively expanding population that requires vastly increased food production on ever-scarcer land resources. Organic produce is often considerably more expensive than conventionally-farmed produce and therefore out of the reach of many if not the majority of families.

How concerned should we be regarding exposure of vulnerable persons to endocrine substances?

Periods of potential increased vulnerability play an important role in the chemical industry's process of research and development of new products and these periods are evaluated carefully. The risks associated with periods of potential increased vulnerability are already integrated into the process of research and development of new products.

To assess the effects of chemicals during 'critical windows' of exposure or 'vulnerable' periods in a life stage, a series of developmental, reproductive and long-term toxicological studies are required before use of the substance is approved under all relevant legislations, such as REACH, Plant Protection Regulation or the Biocidal Product Regulation.

These include multi-generation *in-vivo* studies which look for potential effects on the fertility of the parental generation, as well as an impairment of other potentially vulnerable life stages during development, and of the progeny.

Is it possible to define safety thresholds for endocrine disruptors?

Yes. The safety threshold defines the tipping point under which the body's system is still able to counter-balance an endocrine-mediated effect. Under the effect threshold the substance is therefore endocrine active, rather than endocrine disruptive.

What is dosage and why is it important?

The father of toxicology, Paracelsus, established the now well-known principle that "the dose makes the poison": a product or substance only produces a harmful effect when its dose exceeds a living being's ability to cope with it. A larger dose of some substances can have an adverse effect whereas a smaller dose of the same substance does not: it is the amount that matters.

Dose-effect relationships are determined and examined in assessments of chemicals – including the assessment of the potential endocrine activity of substances. This means that a substance is tested at various concentrations and according to generally-recognized test methods to determine the threshold level, below which effects are considered non-adverse.

[4] TEDX List of Potential Endocrine Disruptors

What is a low-dose effect?

The threshold is determined through the identification of a "no observed adverse effect level" (NOAEL). This is the starting point for defining safe limits of exposure, including acceptable daily intake (ADI) for consumers, or occupational exposure limits (OELs) for workers. It is scientifically defined based on toxicological testing data.

Some scientists however claim to have found effects – though not necessarily adverse – at levels of exposure below the threshold. This is called the "low-dose" hypothesis, and it implies that no threshold can be set for certain substances. Contrary to the low dose theory, there are some substances with endocrine activity, such as some vitamins, where a certain dose is actually necessary to live a healthy life. A deficiency of vitamins (ie a dose that is too low) will cause harmful effects, for example scurvy for insufficient vitamin C, or rickets for insufficient vitamin D. The low-dose hypothesis still remains controversial. Strong scientific consensus based on robust and accepted scientific evidence would be needed before any consideration is given to moving away from the threshold principle which is a key pillar of chemical regulation.

What is potency and why is it important?

The potency of a substance is an essential part of regulatory safety evaluation and is an important factor when establishing safe dosages. Potency is a measure of a substance's strength: at similar dosages, a highly-potent substance produces a greater effect whereas a substance of low potency will produce little or no effect. But even the use of more potent substances can be safe if exposure levels are low: again it is the amount that matters.

Taking potency into account in chemicals legislation (including biocides and pesticides) minimises the probability of making poor regulatory decisions by not distinguishing those substances that are of high concern from those that do not present risks under the conditions in which they are used.

Several Member States, including DE, NL, PL, UK and IRL agree that potency is a vital consideration to be taken into account: "Potency is an intrinsic property of a substance and is critical in hazard identification and characterisation".[5]

How are substances tested for endocrine-disrupting properties?

The EU uses the principle of a tiered testing strategy. If initial studies show reason for concern, additional tests are triggered to further examine and verify these initial findings. Identifying adverse effects in the existing higher-tier studies (even in the absence of knowledge on the mode of action) has allowed regulators to fully assess the risk, resulting in a high level of protection for human health and the environment. The OECD is constantly working to improve the current testing scheme, to adapt this as scientific progress is made, and to account for greater scientific understanding. The industry is fully committed to contributing to any necessary improvement in the current testing requirements.

But are enough data available to assess substances on their possible endocrine-disrupting effects?

Yes. An extensive regulatory system strictly controls what chemicals can be introduced, what experiments can take place, what can be used, for which purpose and how they should be transported, used and disposed of.

[5] Official Irish Position on the Criteria Proposal by the European Commission

Previously, chemicals regulation focussed on the potential for a substance to cause adverse effects, irrespective of how those effects were mediated. Recent changes in legislation, with the inclusion of the endocrine-disruption cut-off criteria in Regulation 1107/2009, places greater emphasis on mode of action. Consequently data packages may now need to be complemented with the inclusion of screening or mode-of-action studies to identify if adverse effects observed are mediated by an endocrine mechanism.

For pesticides in pre-development phase the potential for endocrine disruption is being addressed through internal screening cascades also using in-vitro and in-vivo methods. Substances with endocrine-disrupting reactions are screened out during development.

Are the testing methods also adequate for species in the environment?

Yes. Within vertebrates, the endocrine receptors and pathways are very similar between different taxonomic groups (birds, mammals, amphibians, reptiles and fish). Thus any endocrine-mediated effects are typically already detected by the extensive toxicological data requirements. Additionally, a number of OECD test guidelines for fish have been developed and validated to detect potential endocrine-mediated effects on reproduction or development in partial life-cycle test. Since tests in fish already play an important role in environmental risk assessment and since the hormonal system of fish is well developed, test methods in fish are central for most test strategies.

The sensitivity of terrestrial stages of amphibians or of the many other untested species and groups and mixture toxicity is not an endocrine disruptor specific question, but one of general predictability of ecotox testing and environmental fate estimation.

In contrast to vertebrates, the endocrine system of many invertebrates is less well understood, which is also true for most chemical modes of action in invertebrates. It would be neither feasible nor desirable to elucidate modes of action in large numbers of invertebrate groups for the sake of identifying endocrine effects. However, because of their generally shorter life-cycles, chronic tests with terrestrial and aquatic invertebrates are generally performed in a few indicator species and consider invertebrate reproduction in partial or even full life-cycles. While these tests are not suitable to clarify a mode of action, they can reliably detect the thresholds below which no effect on the population can be expected. Furthermore, the sensitivity of terrestrial stages of amphibians or of the many other untested species and groups and mixture toxicity is not a question specific to endocrine disruptors, but one of general predictability of ecotox testing and environmental fate estimation.

It is said that harmful effects occur due to exposure to mixtures of chemicals at low exposure levels. What are the real risks of “cocktail effects”’ and are they accounted for?

People, animals and the environment are exposed to multiple chemicals at once from a variety of sources. Although the language of “cocktails” is alarming, the presence of chemicals in itself, does not mean that harm is being done.

Modern technology enables us to detect minuscule amounts of substances, but the presence of such a small amount of a specific substance does not mean that it is having any discernible effect on us or on future generations.

The European Food Safety Authority (EFSA) has analysed all studies conducted worldwide on the effects of multiple residues and concluded that *“no assessment of actual cumulative exposure conducted so far has indicated*

any significant risks from exposure to multiple chemicals belonging to a common assessment group where the individual compounds presented no unacceptable risks."[6]

Basically, this means that if the individual component chemicals of a mixture do not constitute a risk, then neither does the mixture. The EFSA is working on the development of a methodology to give additional guidance on the calculation of cumulative exposure.

For the aspect of assessment of chemical mixtures there is no fundamental difference to other modes of action.[7] The opinion of the EU scientific committees from 2011[8] is valid also for endocrine disruption:

1. Chemical mixtures can be addressed via dose/concentration addition.
2. Interactions (including antagonism, potentiation, and synergies) usually occur at medium or high dose levels (relative to the lowest effect levels). This is due to the fact that at a low dose the level of chemicals is usually so insignificant that even a dose addition does not lead to toxicological significance.

What do we want the EU to do?

The mandate of the European Commission as stated in Regulation 1107/2009 and Regulation 528/2012 is to develop a set of criteria (note: not to establish a categorisation system) for the determination of endocrine disrupting properties. The European Commission is likely to prepare horizontal criteria since it believes these will lead to a consistent approach to regulating endocrine disruptors across the different chemical sectors (REACH, Plant Protection Products EC 1107/2009 and Biocides EU 528/2012). However, these sectors have different approaches to the approval process, and therefore inconsistencies are likely to appear: while REACH[9] and the Biocidal Product Regulation (528/2012)[10] include the possibility of taking into account the socio-economic benefits of products and the availability of alternatives which provide for exceptional alternative routes[11], the Plant Protection Product Regulation (1107/2009)[12] approval mechanism will lead to a simple ban with very little room for exceptional alternative routes of approval.

In order for the assessment of endocrine disruptors to be consistent and for all endocrine disruptors to be regulated in the same way, the criteria to identify them must be extensive, and must incorporate scientific fundamentals such as potency, the degree (and timing) of exposure and the determination of thresholds.

If these scientific fundamentals are included, it is possible to clearly define criteria for what is and is not an endocrine disruptor. Thus, categories such as 'suspected' or 'potential' endocrine disruptor are not necessary: a substance either falls under the criteria and is an endocrine disruptor, or it does not.

It is important to get the criteria for endocrine disruption absolutely right. We welcome the public consultation that has taken place and the following impact assessment. We also welcome the European Commission's recommendations that risk assessment, socio-economic considerations and risk-benefit analysis be considered. However we believe that a complete risk assessment option should have been included in the European Commission's proposed options for the criteria.

[6] EFSA Journal (2008) 704, p. 57
[7] EFSA Opinion on Endocrine Disruptors, p. 38
[8] SCHER/SCENIHR/SCCS Toxicity and Assessment of Chemical Mixtures
[9] Use only allowed after granting of authorization per application (adequate control or socio-economic route)
[10] Use only allowed if negligible risk to humans, animals or the environment from exposure to the active substance in a biocidal product, under realistic worst case conditions of use, and if no unacceptable effect
[11] This does not apply for consumer products in biocides
[12] Use only allowed if negligible exposure (human health), i.e. if the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value (396/2005)

What is the crop protection industry calling for?

1. Scientific and realistic regulatory criteria to identify endocrine disruptors

Clear and scientifically-based criteria for endocrine disruptors will lead to higher confidence in the EU as an institution that takes societal concerns seriously, while enabling companies to make business decisions on a reliable basis.

2. The adoption of regulatory criteria that are scientifically valid, unambiguous and practicable, and take the actual risk into account

There should be consideration of the weight of evidence, the potency of the substance and whether exposure to the substance is likely to reach a level where it can cause adverse effects ("threshold"). If not, then there is no relevant health risk.

3. An objective and transparent discussion with all concerned

The topic is emotional and politically sensitive. This is why it is critical that an evaluation of the options for the criteria, in which all stakeholder concerns are addressed, be undertaken on a solid scientific basis.

4. A detailed consideration of unintended consequences

The over-regulation of endocrine disruptors would have far-reaching consequences for trade, innovation, competitiveness and food security.

How will the endocrine disruptor regulation in the EU affect the maximum residue levels (MRLs) for imported commodities?

It is common practice for the European Commission to set maximum residue levels higher than 0.01mg/kg for substances when they are banned within the EU due to a hazard-based cut-off under regulation 1107/2009, effectively allowing for the import of commodities treated with such banned substances. This is possible as the MRL legislation is a risk-based legislation, in line with WTO agreements, as opposed to the hazard-based legislation 1107/2009. If the EU Commission decides to align the two contradicting pieces of regulation, MRLs in commodities produced with active crop protection substances identified under the endocrine cut-off could either be withdrawn entirely or set at a default level of 0.01 ppm, banning the import of those commodities into the European Union.

You say that the carcinogenic, mutagenic or toxic-for-reproduction (CMR) classification system used in the Classification, Labelling and Packaging regulation is not relevant for endocrine disruption. Why?

In February 2013, the General Directorate for Environment submitted a first proposal for a set of criteria for endocrine disruptors. In this proposal, DG Environment chose to model the criteria to identify an endocrine disruptor on CMR classification, creating three different categories into which substances could fall: 'confirmed', 'suspected' and 'potential' endocrine disruptors. However, this model is not appropriate to apply to endocrine disrupting substances. CMR classification represents well-defined adverse effects (such as tumors and malformations) which are suitable for hazard classification. In contrast, the term the term 'endocrine disruption' generically groups different modes of action with the potential to lead to adverse effects of variable nature, severity and concern, and consequently these are not suitable for categorisation.

Categorisation can lead to a number of unintended, negative consequences. It can lead to the creation of blacklists that could include substances which have been approved by the regulatory authorities and are not considered endocrine disruptors. There is also no clear mechanism outlined in the proposal for a substance to be moved from one category to another. Such a mechanism would, once identified, likely involve in-vivo studies, which would unnecessarily increase animal testing and negatively impact substances for which animal testing is not allowed, for example substances used in cosmetics.

If scientifically sound criteria are developed, these should clearly define what is and is not an endocrine disruptor. Categories such as 'suspected' or 'potential' endocrine disruptor are not necessary: a substance either falls under the criteria and is an endocrine disruptor, or it does not.

Has the industry played a big role in delaying the definition and implementation of endocrine-disrupting criteria?

Absolutely not. The industry would have welcomed the implementation of the final criteria by the original legal deadline of December 2013. We have requested a rigorous impact assessment, which will ensure that all aspects of such important legislation are looked at from all angles, and we welcome the Commission's decision to conduct one. Since the December 2013 deadline for establishing criteria was included in legislation that entered into force in 2009, there was ample time to conduct this impact assessment if it had been planned at the outset. Our industry has and will continue to provide constructive input into this process alongside all other stakeholders. At the end of this process we are looking for clear regulatory criteria that distinguish those substances that are of regulatory concern from those that are not.

The most important thing is to get the criteria right.

What is an endocrine disruptor?

"The natural and synthetic chemicals with endocrine activity in laboratory experiments are diverse in terms of structure, properties, and sources. Regardless of their chemical nature, a chemical substance needs sufficient molecular similarity, specificity (affinity), and efficacy to achieve a potency that would interfere with the endocrine system."

Society of Environmental Toxicology and Chemistry: Technical Issue Papers (Setac TIP)

"All current definitions agree that the definition of an "adverse effect" means toxicity, i.e. pathology or functional impairment. Therefore, only a substance that produces toxicity in an intact organism via a hormonal or hormone-like mechanism represents a genuine ED."

Nohynek, J. G., Borgert, J. C., Dietrich, D., Rozman, K.K. (2013) Endocrine disruption: Fact or urban legend?

"Some chemicals, both natural and man-made, can interfere with endocrine glands and their hormones or where the hormones act - the target tissues. These chemicals are called 'endocrine disruptors' […] Endocrine disruption is not, in itself, a measure of toxicity – the occurrence of adverse health effects. Rather, it is considered to be a change that may lead to harmful effects."

GreenFacts

"Many substances, both naturally occurring and man-made, may have some potential to mimic natural hormones under laboratory conditions. […] However, the estrogenic activity of these materials, as measured under laboratory conditions, is generally far below that which is observed for estradiol – the naturally occurring form of œstrogen in the human body."

Cosmetics Europe

"Issues key to understanding the mechanisms of action and consequences of exposure to endocrine disrupting chemicals include age at exposure, latency from exposure, the mixture of chemicals, dose-response dynamics, and long-term latent effects."

The Endocrine Society

"We are concerned that the prevalence of endocrine-related diseases is higher than it has ever been. The disease burden continues to increase in the EU and globally. Evidence is strengthening that environmental factors, including chemical exposures, play a role in these phenomena."

89 Scientists' letter to the European Commission
The 2013 Berlaymont Declaration on Endocrine Disrupters

"Endocrine Disrupting Chemicals (EDCs) are capable to 'disrupt' the hormone system of the human body, which is responsible for the good development and functioning of all vital organs."

Pesticide Action Network Europe

"[…] Endocrine related diseases are increasing at a rate that cannot be attributable to genetic factors alone, and so are likely to involve environmental factors which may include EDCs."

Health and Environment Alliance (HEAL)
Health costs in the European Union: how much is related to EDCs?

"If the EU population were being exposed unwittingly to harmful levels of oestrogen mimicking and anti-androgenic compounds, the possible predictable effects of this would include: - an increase in hormone related cancers […], effects on sperm, increased rates of birth defects of the reproductive tract, and girls coming to puberty earlier. It is rather chilling that all these effects do appear to be happening, and it is this whole picture, rather than one particular effect taken in isolation, that leads many scientists to suggest that endocrine disrupting chemicals (EDCs) are causing, or at least partly to blame, for these effects."

World Wild Fund (WWF)
Response to the community strategy for endocrine disruptors

How should endocrine disruptors be regulated?

"Furthermore, to inform on risk and level of concern for the purpose of risk management decisions it is the opinion of the SC that risk assessment (taking into account hazard and exposure data/predictions) makes best use of available information. EDs can therefore be treated like most other substances of concern for human health and the environment, i.e. be subject to risk assessment and not only to hazard assessment."

European Food Safety Authority

Scientific Opinion on the hazard assessment of endocrine disruptors: Scientific criteria for identification of endocrine disruptors and appropriateness of existing test methods for assessing effects mediated by these substances on human health and the environment

"We […] are writing to draw your attention to imminent decisions by the European Commission to set a regulatory framework for so-called endocrine disrupting chemicals. We are concerned that the approach proposed could rewrite well-accepted scientific and regulatory principles in the areas of toxicology and ecotoxicology without adequate scientific evidence justifying such a departure from existing practices."

Scientists' Letter to Anne Glover, Chief Scientific Adviser to the President of the European Commission

"It is critical to move beyond the piecemeal, one chemical at a time, one disease at a time, one dose approach currently used by scientists studying animal models, humans or wildlife."

World Health Organisation (WHO) & United Nations Environment Programme (UNEP)
State of the Science of Endocrine Disrupting Chemicals 2012

"Many policy-makers, however, are not aware of EDCs and that existing EU regulations already contain procedures for addressing them in national legislation. Public authorities in charge of public health protection and food and product safety also need to be better informed about EDCs."

Women in Europe for a Common Future (WECF)
Child Protect project

"Most animal tests involve repeated high-dose exposure to a single test chemical. This fails to mimic the human experience of repeated, low-dose exposure to many chemicals over a lifetime."

"An enormous body of information already exists—much of which is relevant to endocrine activity […] Both pesticides and High Production Volume (HPV) chemicals undergo extensive animal testing"

People for the Ethical Treatment of Animals (PETA)

"The currently drafted EU framework for EDCs foresees a priori regulation of agents that may show presumably endocrine-mediated effects in sole experimental system. […] This approach is based on a very small number of publications that lack the required scientific robustness […], will set an unforeseen precedence, and finally will have profound ramifications for everyone's' livelihood."

Letter of 18 editors of editors of prominent journals of pharmacology and toxicology

"Many substances, be they natural or man-made, are endocrine-active. Think for example, a 200 g meal of carrots contains 800 times more estrogen-like compounds than the same amount of food that was in contact with a BPA-based polycarbonate container. Despite the endocrine activity displayed by a vegetable like carrots, no one would call carrots an endocrine disruptor!"

BPA Coalition