Exposure to environmental factors and cancer risk
Scientific knowledge to improve prevention and regulation

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Disclaimers

• I only receive financial support from national and European public institutions.

• I have no conflict of interests to report.

• The views expressed here are my own and do not necessarily represent the position of Inserm.
Cancer Hallmarks

External influences

- Resisting cell death
- Evading growth suppressors
- Inducing angiogenesis
- Activating invasion and metastasis
- Enabling replicative immortality
- Sustaining proliferative signaling

Body

(Hanahan & Weinberg, Cell, 2011)
Estimates of *heritability* from twin studies: Indirect but **strong evidence for non-genetic influences**

<table>
<thead>
<tr>
<th>Disease or trait</th>
<th>Disease heritability*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 diabetes</td>
<td>90 %</td>
</tr>
<tr>
<td>Eye colour</td>
<td>80 %</td>
</tr>
<tr>
<td>Skin melanoma</td>
<td>58 %</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>53 %</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>30-60 %</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>25 - 30 %</td>
</tr>
<tr>
<td>Testis cancer</td>
<td>25 %</td>
</tr>
<tr>
<td>Nervous system cancer</td>
<td>12 %</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>8 %</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>≈ 1 %</td>
</tr>
</tbody>
</table>

*Heritability is the share of the variation in the disease risk in the population due to genetic factors. Its estimates are specific to the population, disease and circumstances on which it is estimated. (Tenesa and Haley, *Nat Rev Genet*, 2013)
More direct evidence - Oestrogen-related factors likely associated with breast cancer risk

**Estrogenic drugs**
- DES/diethylstilboestrol (intra-uterine or adult exposures)
- Hormonal substitution therapy (adulthood)
- Tamoxifen (anti-oestrogenic drug against breast cancer)

**Reproductive life factors related to oestrogen exposure**
- Low number of pregnancies
- Early menarche, late menopause
- Short total breastfeeding duration

**Synthetic oestrogen-like chemicals**
- DDT (following early-life exposure)
- Bisphenol A (likely)
- Total xenoestrogenic burden
What does “Chemical A causes disease B” mean?

- Cancers are *multifactorial diseases*
  - A few (historical?) exceptions exist: asbestos can be considered as a *necessary cause* of mesothelioma

- However, for most cancers, in the EU today, the controllable causes of environmental origin are likely to correspond to a possibly large number of environmental factors each having a “small” contribution (i.e. many hazards each contributing to a small fraction of the overall *risk*).

- **Practical implications for prevention**
  From a prevention perspective, this implies to develop (e.g. regulatory) tools able to simultaneously cope with a large number of risk factors.
  Here, the concept of *hazard class* (CLP regulation, 1272/2008) can be very relevant
From hazard identification to prevention measures

Hazard identification *(science)*

Prevention measures *(policy)*

Grouping of factors into relevant hazard classes *(agencies)*

E.g. laws, labelling of products...

Carcinogens
Mutagens
Reprotoxicant
PBT (Persistent, Bioaccumulative, toxic)
vPvB (very Persistent, Bioaccumulative, toxic)
Endocrine Disruptors

The world of chemical and physical factors

>23,000 marketed substances *(source: ECHA)*
Example of the EU regulations on endocrine disruptors (EDs)

<table>
<thead>
<tr>
<th>Definition of EDs</th>
<th>Test requirements</th>
<th>Risk management logic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plant protection products</td>
<td>Y</td>
<td>I</td>
</tr>
<tr>
<td>Biocides</td>
<td>Y</td>
<td>I</td>
</tr>
<tr>
<td>REACH chemicals</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Cosmetics</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Food additives</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Food packaging</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Workers’ regulations</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Air, drinking water</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

ED report conclusions (2019):
Lack of cross-sectorial definition of EDs
- The application of the WHO definition of endocrine disruptors “across all legislation” (EC, 2020) would solve this problem

Risk incurred by EDs managed differently in various sectors (sector-specific risk management logics)
- EC wishes to ban EDs in consumer products (EC, 2020)

(Demeneix & Slama, report to the EU Parliament, 2019)

I: Insufficient/needs reinforcement. N: None or very limited. Y: Yes, satisfying existing regulation.
The risk management logics of carcinogens is heterogeneous across sectors.

<table>
<thead>
<tr>
<th>Sector</th>
<th>Definition of carcinogens</th>
<th>Risk management logic</th>
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</thead>
<tbody>
<tr>
<td>Plant protection products</td>
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The unjustifiable anomaly of Particulate Matter (PM$_{2.5}$) EU regulation.
In summary

• For many cancers, purely genetic factors (genetic polymorphisms) are unlikely to be the main causal agents

• “External” factors are likely to play a large role in cancer risk at the population level

• For many cancers today, the likely causal model is that of many controllable hazards each contributing to a small fraction of the overall risk

• Handling chemical and physical risk factors by groups (via the hazard class concept) is relevant from a public health perspective and efficient

• Banning specific hazard classes such as carcinogens (and endocrine disruptors) from consumers products and sectors with potential exposure of the general population and susceptible subgroups would be relevant: “generic approach to risk management” (EC Chemicals strategy for sustainability, 2020)

• This implies to strongly support the agencies in charge of identifying the substances belonging to each hazard class of concern (ECHA, EFSA...) and probably increasing the requirements regarding the tests to conduct before marketing a substance
Thank you for your attention
Identifying “safe levels” of exposure is not a realistic expectation

• It is not possible to accurately predict the effect of an ED ignoring a subject’s exposure to other EDs (“concentration addition” logic)
• Non-monotonous dose-response functions of hormones (and likely of some EDs)
• Effects of hormones and EDs observed at very low doses
• Some tests of endocrine activity are not very sensitive (e.g., uterotrophic assay) (Markey C, EHP, 2001)
• EU regulations push for more limited reliance on animal testing
• Observed thresholds for effects generally correspond to “experimental thresholds” rather than to “biological thresholds” (which cannot be scientifically demonstrated)
Regulation of fine particulate matter (PM$_{2.5}$) yearly levels
Generic approach to risk management (definition)

• In the EU legislative framework for chemicals, a ‘generic approach to risk management’ is an automatic trigger of predetermined risk management measures (e.g. packaging requirements, restrictions, bans, etc.) based on the hazardous properties of the chemical and generic considerations of their exposure (e.g. widespread uses, uses in products destined to children, difficult to control exposure).

• It is applied in a number of pieces of legislation on the basis of specific considerations (e.g. characteristics of the hazard, vulnerability of certain population groups, non-controllable or widespread exposure). SWD(2019) 199.

EC, COM(2020) 667 Chemicals strategy for sustainability towards a toxic-free environment