Exposure to environmental factors and cancer risk

Scientific knowledge to improve prevention and regulation

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La science pour la santé
From science to health

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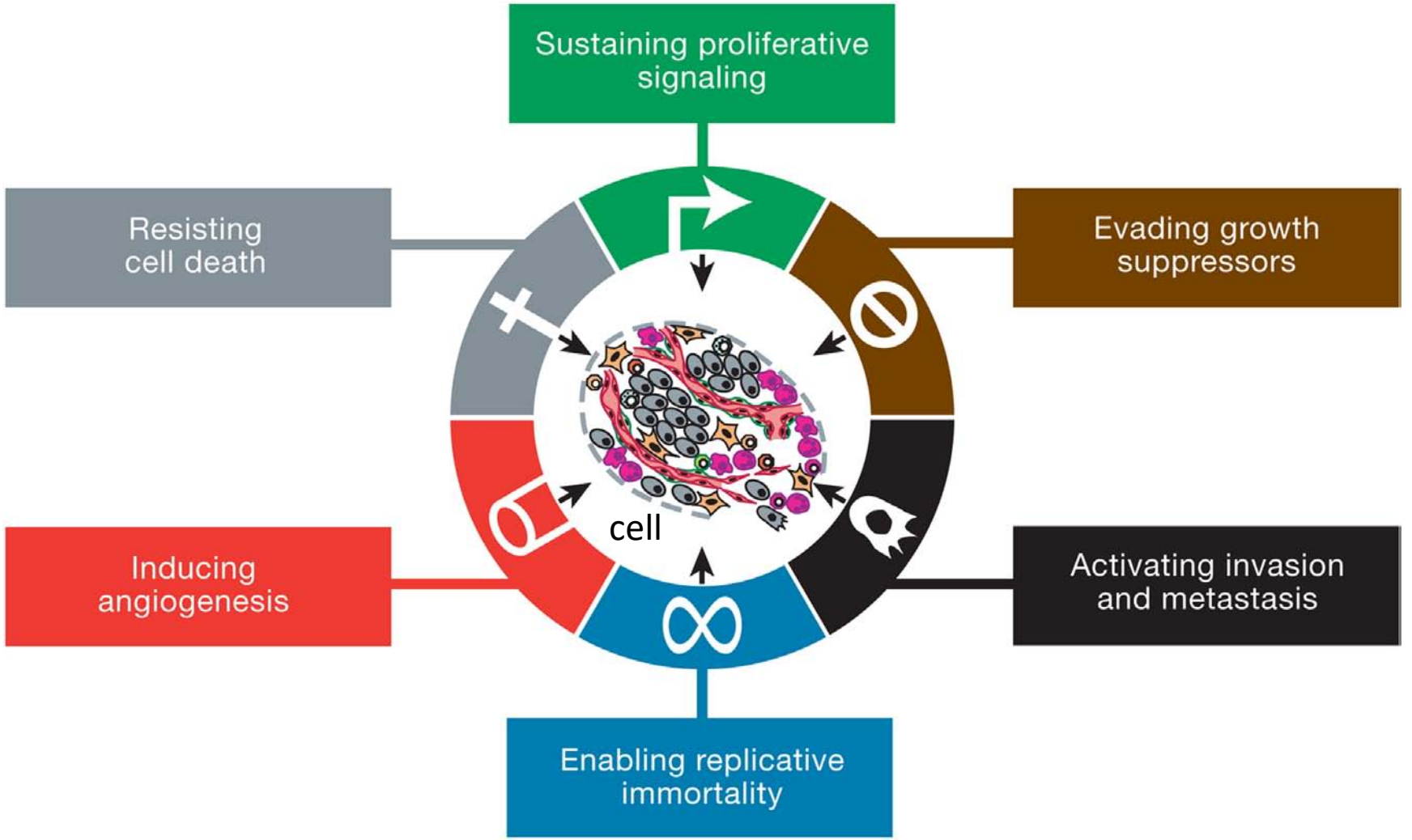
iAB
EPIGENETICS
CHRONIC DISEASES
CANCER

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



Body

(Hanahan & Weinberg, *Cell,* 2011)

Estimates of *heritability* from twin studies: Indirect but **strong evidence for non-genetic influences**

Disease or trait	Disease heritability* As estimated by twin studies
Type 1 diabetes	90 %
Eye colour	80 %
Skin melanoma	58 %
Thyroid cancer	53 %
Type 2 diabetes	30-60 %
Breast cancer	25 - 30 %
Testis cancer	25 %
Nervous system cancer	12 %
Lung cancer	8 %
Leukaemia	≈ 1 %

For these diseases with heritability between 1 and about 50%, a large role of environmental (including behavioural) factors is expected

Most figures from (Visscher et al, *AJHG*, 2012) and Mucci et al., *JAMA*, 2016 (melanoma) ; see Slama, Le Mal du Dehors (Quae, 2017) for other references

*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

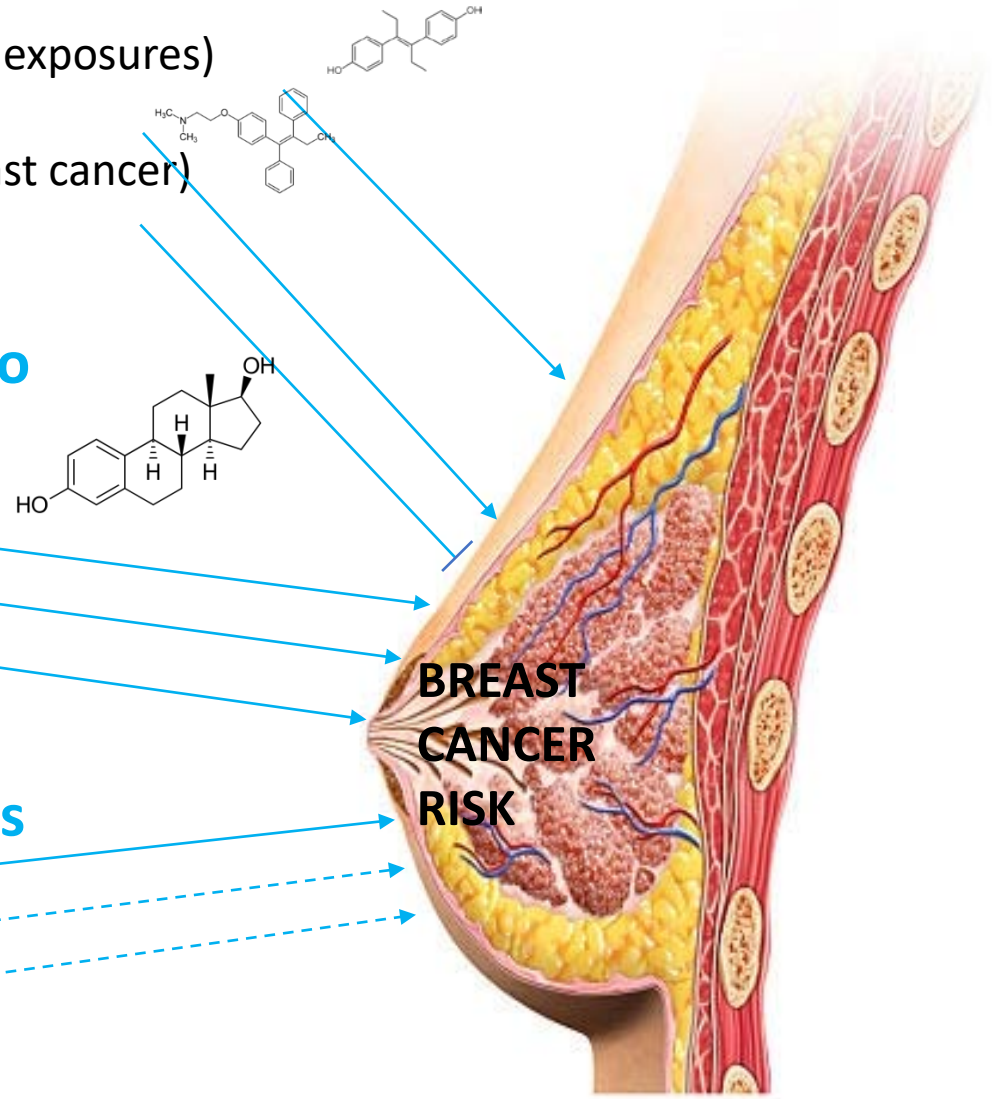
DES/diethylstilboestrol (intra-uterine or adult exposures)
Hormonal substitution therapy (adulthood)
Tamoxifen (anti-oestrogenic drug against breast cancer)

Reproductive life factors related to oestrogen exposure

Low number of pregnancies
Early menarche, late menopause
Short total breastfeeding duration

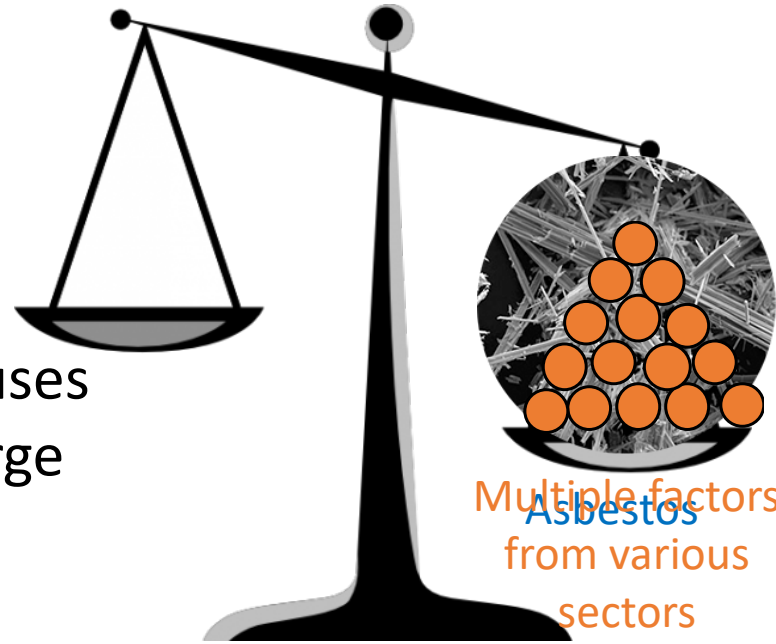
Synthetic oestrogen-like chemicals

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



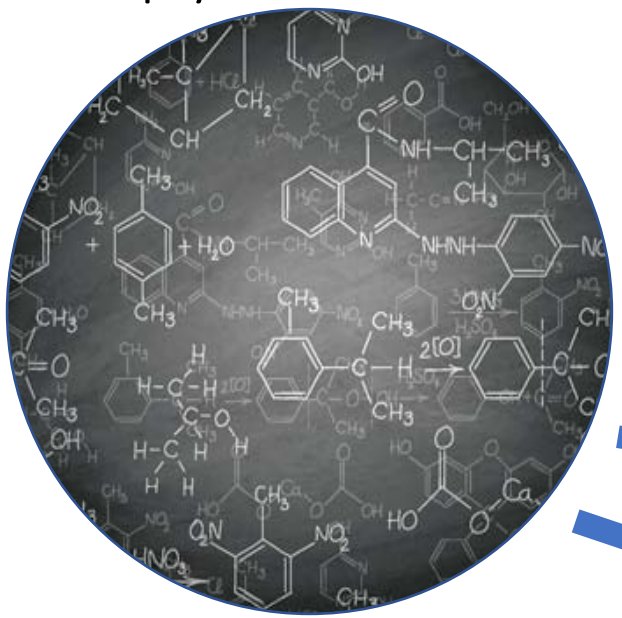
Mesothelioma (cancer of the lining of the lungs)

- 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

The world of chemical and physical factors



>23,000 marketed substances

(source: ECHA)

Hazard identification *(science)*

Grouping of factors into relevant hazard classes (agencies)

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

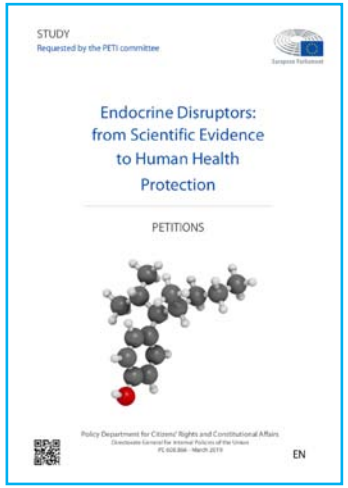
Prevention measures *(policy)*

E.g. laws, labelling of products…

Example of the EU regulations on endocrine disruptors (EDs)

	Definition of EDs	Test requirements	Risk management logic
Plant protection products	Y	I	Y
Biocides	Y	I	Y
REACH chemicals	I	I	I
Cosmetics	N	N	N
Food additives	N	N	N
Food packaging	N	N	N
Workers' regulations	N	N	N
Air, drinking water	N	N	Y

I: Insufficient / needs reinforcement. N: None or very limited. Y: Yes, satisfying existing regulation.



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

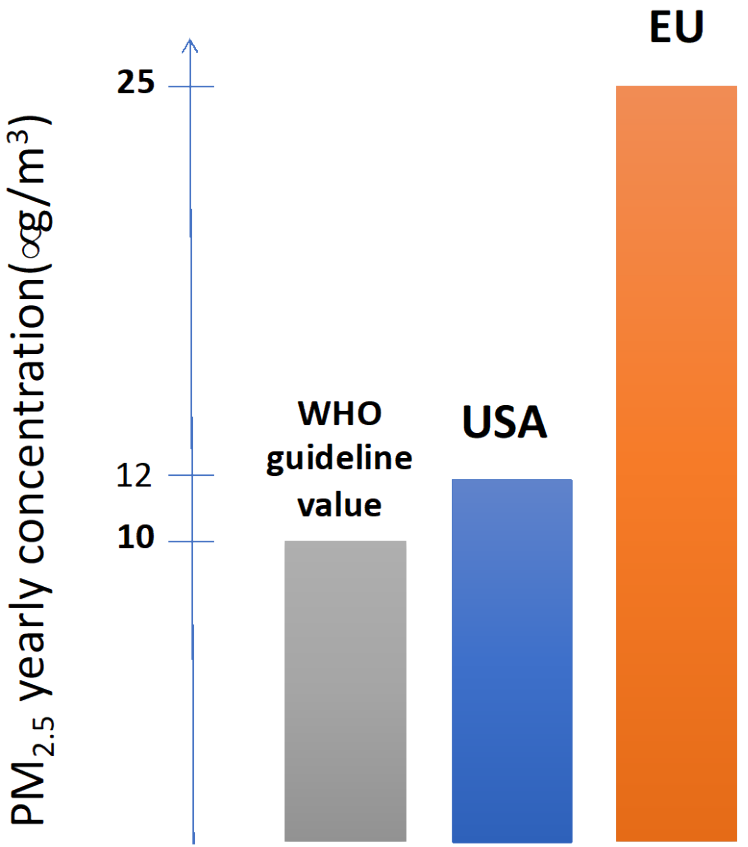
Risk incurred by EDs managed differently in various sectors (sector-specific risk management logics)

- EC wishes to ban EDs in consumer products (EC, 2020)

(Demeneix & Slama, report to the EU Parliament, 2019)
http://www.europarl.europa.eu/thinktank/fr/document.html?reference=IPOL_STU(2019)608866

The risk management logics of carcinogens is heterogeneous across sectors

	Definition of carcinogens	Risk management logic
Plant protection products	Y	Y
Biocides	Y	Y
REACH chemicals	Y	I
Cosmetics	Y	Y
Food additives	Y	N
Food packaging	Y	N
Air	N	N



The unjustifiable anomaly of Particulate Matter ($PM_{2.5}$) EU regulation

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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

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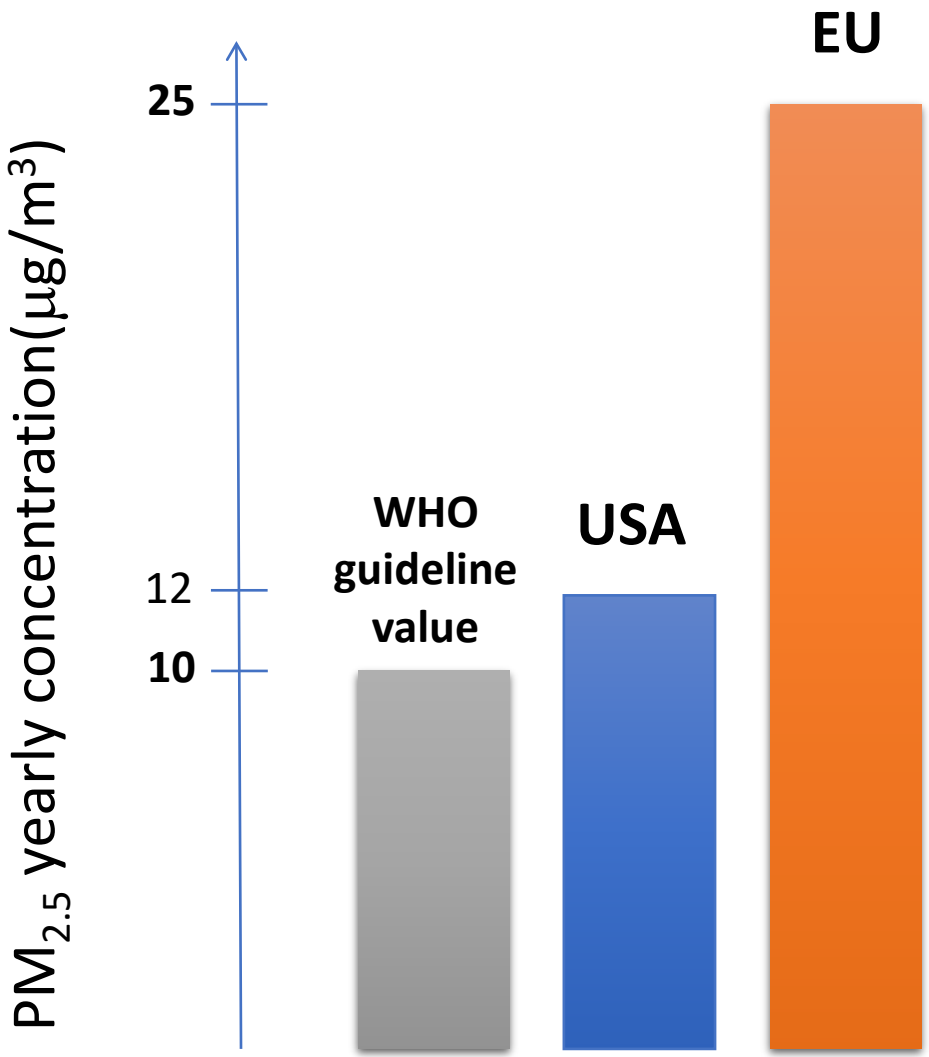
Identifying “safe levels” of exposure is not a realistic expectation

- 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