Basic properties and molecular mechanisms of exogenous chemical carcinogens

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Recent advances in biochemistry and molecular biology in characterizing chemical carcinogenesis

Method improvement
- Experimental induction of cancers
- DNA adduct quantification in humans
- Genome sequencing
- Epigenomics
- Polymorphism genetics

Mutagenesis
- Cataloguing oncogens and tumor suppressor genes
- Clonal (driver) versus non-clonal mutations
- Exogenous versus endogenous mutagenesis
- Mechanisms of DNA adduction
- Site-specific versus non-site-specific adduction
- Biological effects of free radicals

Biochemistry and molecular biology
- Metabolism of xenobiotics
- Low-dose versus high-dose carcinogenesis
- Cataloguing environmental carcinogens
- Bioaccumulation of exogenous carcinogens in the adipose tissue
Cancer as a Model
**Is the growing incidence of cancers related to aging?**

*Common interpretation:*

Because cancer incidence increases with life expectancy increase, cancer growing incidence is due to aging

*New interpretation:*

1. Cancer incidence increases with the duration of exposure to exogenous factors: *the longer the duration of exposure is, the higher the risk of developing cancer is.*

2. Cancer incidence is not restricted to any particular age group

3. The growth rate for childhood cancers incidence is on average at 1.1% yearly over the past 30 years.


*Window period of exposure.*

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Over the last 20 years, there have been more than an increase of 1% of cancers in children every year.

Cancer incidence in children aged 0-14 years in Europe
Initiation corresponds to the first genetic and/or epigenetic event leading “normal” cells to mutate. Promotion is characterized both by the reversibility of the clonal proliferative expansion of initiated cells and by the progressive evolution of genetic and epigenetic changes, leading the clone of preneoplastic cells to reach a critical number of mutations and therefore the irreversible state of progression.
Sequencing analysis of the human genoma

There cannot be a cancer without a critical number of driver mutations

Except smoking, all classical lifestyle-related factors are not mutagenic. Most of them may act as promoters or cocarcinogens.¹

✓ **Tobacco smoking:** equivalent of a complete carcinogen

✓ **Alcohol:** cocarcinogenic

✓ **Diet imbalance, ingestion of animals fats:** no proven epidemiological link. No evidence of mutagenic effect

✓ **Overweight/obesity:** adipose tissue may act as a reservoir for environmental carcinogens²,³

✓ **Hormones, contraception, post menopausal treatment:** promotors

✓ **Stress:** mechanism unknown

✓ **Sedentarity:** mechanism unknown

Initiators and progressors and more specifically mutators are the main contributors to carcinogenesis, because they allow carcinogenesis to reach an irreversible state. Since less than 5% of overall cancers are estimated to be hereditary and 25-30% causally related to the complete carcinogenic effect of tobacco smoking, we estimate that overall the Population Attributable Fraction (PAF) for environmental carcinogens mutagenic range from 65-75%, while PAF for non mutagenic factors (i.e. for promoters and cocarcinogens), may range from 40-60% according to previous Doll and Peto's estimate.
Xeno-chemicals, be they mutators, promoters or cocarcinogens may be therefore involved in the present growing incidence of cancer in high income countries.
Exogenous chemical carcinogenesis is an extremely complex multifactorial process during which gene–environment interactions involving chronic exposure to exogenous chemical carcinogens (ECCs) and polymorphisms of cancer susceptibility genes add further complexity.
Basic properties and molecular mechanisms of exogenous chemical carcinogens

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Exogenous chemical carcinogenesis is an extremely complex multifactorial process during which gene-environment interactions involving chronic exposure to exogenous chemical carcinogens (ECCs) and polymorphisms of cancer susceptibility genes add further complexity. We describe the properties and molecular mechanisms of ECCs that contribute to induce and generate cancer. A basic and specific property of many lipophilic organic ECCs including polycyclic aromatic hydrocarbons and polyhalogenated aromatic hydrocarbons is their ability to bioaccumulate in the adipose tissue from where they may be released in the blood circulation and target peripheral tissues for carcinogenesis. Many organic ECCs are procarcinogens and consequently need to be activated by the cytochrome P450 (CYP) system and/or other enzymes before they can adduct DNA and proteins. Because they contribute not only to the cocarcinogenic and promoting effects of many aromatic pollutants but also to their mutagenic effects, the aryl hydrocarbon receptor-activating and the inducible CYP systems are central to exogenous chemical carcinogenesis. Another basic property of ECCs is their ability to induce stable and bulky DNA adducts that cannot be simply repaired by the different repair systems. In addition, following ECC exposure, mutagenesis may also be caused indirectly by free-radical production and by epigenetic alterations. As a result of complex molecular interplays, direct and/or indirect mutagenesis may especially account for the carcinogenic effects of many exogenous metals and metalloids. Because of these molecular properties and action mechanisms, we conclude that ECCs could be major contributors to human cancer, with obviously great public health consequences.

In a review and perspective paper, chemical carcinogenesis has been mainly described on the basis of the endogenous hypothesis (5). This prompted us to systematically review experimental data suggesting that another concept is possible, i.e. that exogenous chemical carcinogens (ECCs) which result from tobacco smoking or from involuntary exposure to environmental chemicals may also be important contributors to carcinogenesis, as it is for micro-organisms and ionizing radiation.

We define exogenous carcinogens as all types of physical, chemical and biological agents that can cause cancer after having penetrated into the organism by respiratory, digestive, cutaneous or other possible contamination routes. We define endogenous carcinogens as all potentially carcinogenic molecules or metabolic intermediates that arise in the organism as a consequence of respiration and/or food intake in people living in a safe non-polluted environment. We exclude active tobacco smoking from the definition of environmental exposure but we include in the definition of environmental chemical carcinogens not only carcinogens resulting from occupational activities and more generally from industrial pollution but also carcinogens that are associated with passive tobacco smoking or overcooking meat. We thus consider overall that ECCs encompass chemicals resulting from active tobacco smoking or from involuntary environmental exposure.

In the present paper, we describe the different properties and molecular mechanisms of exogenous chemicals that contribute to induce and generate cancer, and we discuss the hypothesis according to which these properties and mechanisms may make exogenous chemicals more prone to cause cancer than endogenous natural molecules.

Models of carcinogenesis

Carcinogenesis can be modeled in two stages, ‘initiation’ and ‘promotion’ (6,7). In 1954, Rous (8) individualized a third stage that...
Initiation corresponds to the first genetic and/or epigenetic event leading “normal” cells to mutate. Promotion is characterized both by the reversibility of the clonal proliferative expansion of initiated cells and by the progressive evolution of genetic and epigenetic changes, leading the clone of preneoplastic cells to reach a critical number of mutations and therefore the irreversible state of progression.
Categorization of some environmental chemicals according to their carcinogenic and/or cocarcinogenic properties (1/2)

<table>
<thead>
<tr>
<th></th>
<th>Mutagen</th>
<th>Promoter</th>
<th>Cocarcinogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acrolein</td>
<td>M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetylaminofluorene</td>
<td>M</td>
<td>P</td>
<td>C</td>
</tr>
<tr>
<td>Air fine particles</td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Arylamines</td>
<td>M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asbestos</td>
<td>M</td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Azoic dyes</td>
<td>M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisphenol A</td>
<td>M</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>β Naphylamine</td>
<td>M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzene and related</td>
<td>M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>molecules</td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>1,3-Butadiene</td>
<td>M</td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Phthalates</td>
<td>M</td>
<td>P</td>
<td></td>
</tr>
</tbody>
</table>
Categorization of some environmental chemicals according to their carcinogenic and/or cocarcinogenic properties (2/2)

<table>
<thead>
<tr>
<th></th>
<th>Mutagen</th>
<th>Promoter</th>
<th>Cocarcinogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dioxins</td>
<td>M</td>
<td>P</td>
<td>C</td>
</tr>
<tr>
<td>Formaldehyde and other related molecules</td>
<td>M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormonal residues</td>
<td>M</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>Metals, metalloids</td>
<td>M</td>
<td>P</td>
<td>C</td>
</tr>
<tr>
<td>NOCs</td>
<td>M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>M (some)</td>
<td>P</td>
<td>C</td>
</tr>
<tr>
<td>PHAHs</td>
<td>M (some)</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>PAHs</td>
<td>M</td>
<td>P</td>
<td>C</td>
</tr>
<tr>
<td>PCBs</td>
<td>M (some)</td>
<td>P</td>
<td>C (some)</td>
</tr>
<tr>
<td>Pesticides</td>
<td>M (some)</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>Vinyl chlorides (monomers)</td>
<td>M</td>
<td>P</td>
<td></td>
</tr>
</tbody>
</table>
## Some categories of pharmaceuticals and cosmetics with presumed or proved carcinogenic properties in humans

<table>
<thead>
<tr>
<th>Category</th>
<th>Anti-estrogens</th>
<th>Endometrium carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticancer drugs</strong></td>
<td>Alkylating agents</td>
<td>Leukemia, lymphoma, sarcoma, breast cancer and other solid tumors</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>ND</td>
</tr>
<tr>
<td><strong>Common pharmaceuticals</strong></td>
<td>Oral contraceptives</td>
<td>Breast cancer</td>
</tr>
<tr>
<td></td>
<td>Hormone replacement therapy</td>
<td>Breast cancer</td>
</tr>
<tr>
<td></td>
<td>Cholesterol-lowering drugs*</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>Other medicines*</td>
<td>ND</td>
</tr>
<tr>
<td><strong>Cosmetics</strong></td>
<td>AAs (hair dyes)</td>
<td>Bladder cancer</td>
</tr>
<tr>
<td></td>
<td>Paraben</td>
<td>Breast cancer</td>
</tr>
</tbody>
</table>

*Carcinogenic in the 2 year rodent carcinogenesis bioassay, but not proved to be carcinogenic in humans*

*Irigaray and Belpomme 2010 Carcinogenesis*
A basic and specific property of many lipophilic organic ECCs including polycyclic aromatic hydrocarbons and polyhalogenated aromatic hydrocarbons is their ability to bioaccumulate in the adipose tissue from where they may be released in the blood circulation and target peripheral tissues for carcinogenesis.
Low dose chemical pollutants in diet and air

Ingestion, inhalation

Storage in adipose tissue

Adipose tissue

Permanent release in blood stream

Mutation and/or Promotion in peripheral tissue(s)

Carcinogenesis in peripheral tissue(s)

Inhibition of lipolysis IMC↑

Insulin and adipokines

Promotion in peripheral tissue(s) (Breast)

Irigaray P. Adipokines and cancer. 30th ESPEN Congress, 13-16 Septembre 2008, Florence, Italie
Irigaray P. Hydrocarbons: Pollution, Health Effects and Chemistry, Novascience, Polymer Science and Technology, 2010
CMR SUBSTANCES TRANSFER TO THE PLACENTA: SEVERAL HUNDREDS OF THEM CONTAMINATE NEWBORNS


www.artac.info
Another basic property of ECCs:

their ability to induce stable and bulky DNA adducts that cannot be simply repaired by the different repair systems.

Following ECC exposure, mutagenesis may also be caused indirectly by free-radical production and by epigenetic alterations.
Representation of a dose dependent hypothetic relationship between oxygen free radicals and cancer genesis

Local doses of free radicals capable of cancer genesis are infratoxic. Doses capable of inducing promotion seems lower than those involved in mutagenesis.
ECCs do not only contribute to direct mutagenesis by adducting to DNA. They can also modify molecular metabolic pathways and cell signals generally by altering protein, RNA and protein expression, hence inducing epigenetic changes and therefore contributing to indirect mutagenesis.

 Metals and metalloids.

In addition to exogenous organic chemicals, several metals and metalloids have been rated as certain or probable carcinogens by International Agency for Research on Cancer, albeit their mechanism of action is far less clear.

As a result of complex molecular interplays, direct and/or indirect mutagenesis may especially account for the carcinogenic effects of many exogenous chemicals in people with polymorphic susceptibility genes.
Some candidates of polymorphic susceptibility genes that may influence exogenous chemical carcinogenesis in humans

<table>
<thead>
<tr>
<th>Type of gene</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I polymorphisms</td>
<td>CYP1A1, CYP1A2, CYP2A6, CYP1B1, CYP2D6,</td>
</tr>
<tr>
<td></td>
<td>CYP2E1, CYP3A4, MPO, EPHX1</td>
</tr>
<tr>
<td>Phase II polymorphisms</td>
<td>GSTM1, GSTT1, GSTP1, NAT1, NAT2, NQO1,</td>
</tr>
<tr>
<td></td>
<td>SULT1A1, SOD2</td>
</tr>
<tr>
<td>ABC polymorphisms</td>
<td>MRP2/ABCC2</td>
</tr>
<tr>
<td>DNA repair genes</td>
<td>XRCC1, XRCC3, XPD, XPF, ERCC1</td>
</tr>
<tr>
<td>Cell cycle control genes</td>
<td>TP53, HRAS</td>
</tr>
</tbody>
</table>
Conclusion

Identifying the causes of cancer would have considerable public health consequences ranging from primary prevention to screening, early diagnosis and treatment. Because many exogenous chemicals are lipophilic, bioaccumulate in the adipose tissue, metabolize into DNA-reactive by-products, form stable and bulky DNA adducts, induce free radicals and/or act through epigenic mechanisms and, consequently, due to all these properties, can be highly mutagenic through direct or indirect mechanisms, we believe that they may be major contributors to carcinogenesis in humans.
In summary

Because of these molecular properties and action mechanisms, we conclude that ECCs could be major contributors to human cancer, with obviously great public health consequences.
Xeno-chemicals, many are CMR molecules

- Chemical substances on the European market
- Chemical substances included in REACH.
- Chemical substances tested for their hazardous properties.

[www.artac.info]
3 articles

Article 1: The development of numerous current diseases is a result of the deterioration of the environment.

Article 2: Chemical pollution represents a serious threat to children and to Man's survival.

Article 3: As our own health, that of our children and future generations, is under threat, the Human race itself is in serious danger.
The Paris Appeal has been signed by:

• over 1,000 scientific key figures,
• 1,500 NGOs,
• approx. 250,000 European citizens,
• the Standing Committee of European Doctors which gather all governing medical bodies and other medical organizations, representing the 2 million medical doctors in the 25 EU Member States.
Protect Women and Children:
2 million medical doctors call out to Euro-deputies

For the Paris Appeal Support Committee
www.artac.info (appel de paris)
www.ipetitions.com/petition/paris-appeal
Children’s Health and the Environment
12-13 April 2011 in UNESCO in Paris
Followed by a two-day international intensive

Course of Environmental Medicine
14-15 April 2011 in UNESCO in Paris
First Session:
  Cancer and the environment

Second Session:
  Childhood at risks

Third Session:
  The environmental origin of today’s public plague

Fourth Session:
  Civil Society and European institutions in protecting children’s health

For more information on the congress or course please visit: [ww.artac.info](http://www.artac.info) (Colloque)
Thank you for your attention

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