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# Carcinogénesis Química

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Oncología Molecular
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# Objetivos

- Conocer definiciones, clasificaciones y conceptos relevantes de la carcinogénesis química
- Conocer algunas sustancias carcinogénicas y su asociación con enfermedades malignas específicas
- Comprender los mecanismos involucrados: exposición, absorción, activación metabólica

# Datos Epidemiológicos

- Enfermedad en mineros ("wasting disease") (Paracelso 1567)
- Cáncer nasal por inhalación de tabaco (Hill 1761)

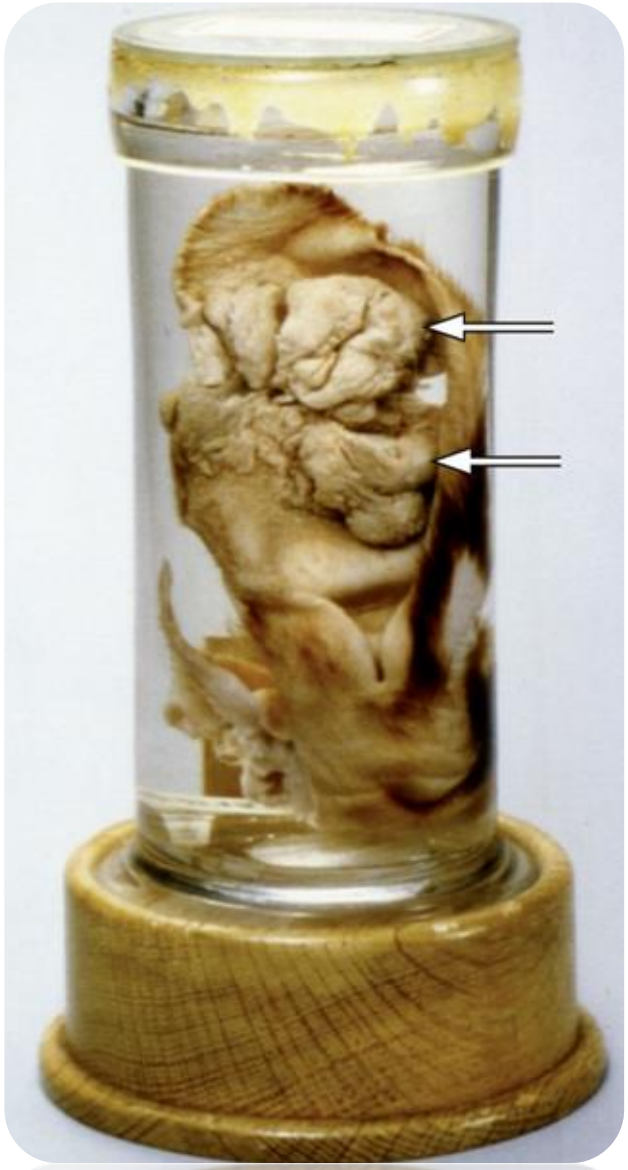
- Cáncer escroto en deshollinadores de chimenea (Pott 1775)
- Cáncer oral en fumadores (Bouisson 1859)

- Cáncer de vejiga en trabajadores de fábrica de anilinas (Rehn 1895)
- Otros (radio, rayos X)

# Modelo de Inducción Química

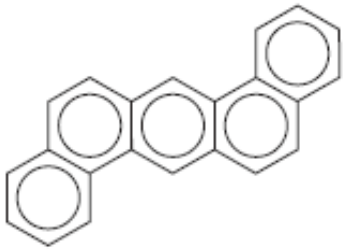
- Primer modelo experimental: alquitrán de carbón
- Aplicado sobre orejas de conejo durante > 1 año

Yamagiwa (1915)

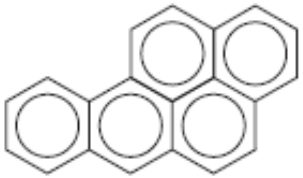


# Carcinógenos: Hidrocarburos

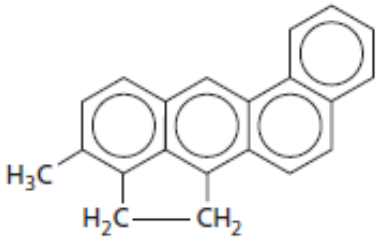
- Producidos por combustión incompleta de material orgánico



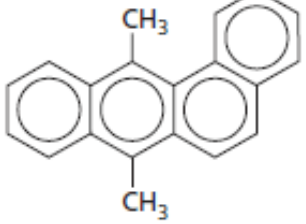
dibenz[*a*,*h*]anthracene



benzo[a]pyrene




3-methylcholanthrene




7,12-dimethylbenz[a]-anthracene

**PAH**

PubChem: https://pubchem.ncbi.nlm.nih.gov/

Biology of Cancer 2013. R. Weinberg

# Carcinogénos Químicos

Table 1 | **Selected human chemical carcinogens**

| Compounds* | Main sources/uses | Affected organs/cancer type |
|---|---|---|
| ***Aminoazo dyes*** | | |
| *o*-Aminoazotoluene | Pigments; colouring oils; immunosuppressant | Liver, lung, bladder |
| *N*,*N*-dimethyl-4-aminoazobenzene | Colour polishes; waxes (no longer in use) | Lung, liver |
| ***Anticancer drugs*** | | |
| Melphalan | Chemotherapy | Leukaemia‡ |
| Thiotepa | Chemotherapy (no longer in use) | Leukaemia‡ |
| ***Aromatic amines/amides*** | | |
| 2-Naphthylamine | Dyes; antioxidant (no longer in use) | Bladder‡ |
| 4-Aminobiphenyl | Dyes; antioxidant (no longer in use); research tool | Bladder‡ |
| 2-Acetylaminofluorene | Model compound; tested as a pesticide | Liver, bladder |
| ***Aromatic hydrocarbons*** | | |
| Benzo[*a*]pyrene | Coal tar; roofing; cigarette smoke | Skin, lung, stomach |
| 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin | No commercial use; tested as a pesticide | Lung‡, lymphoma‡, liver |
| Polychlorinated biphenyls | Flame retardants; hydraulic fluids | Liver, skin‡§ |
| ***Metals (and compounds)*** | | |
| Arsenic | Natural ores; alloys; pharmaceutical agent | Skin‡, lung‡, liver‡ bladder |
| Cadmium | Natural ores; pigments; batteries; ceramics | Lung‡, prostate‡, kidney‡ |
| Nickel | Natural ores; alloys; electrodes; catalysts | Lung‡, nasal cavity‡ |

Luch 2005. Nature Rev Cancer 5: 113-25

# Carcinogénos Químicos

| | | |
|---|---|---|
| ***Natural carcinogens*** | | |
| Aflatoxin $B_1$ | A mycotoxin (found in contaminated food) | Liver‡ |
| Asbestos (fibrous silicates) | Thermal insulation; gaskets (declining usage) | Lung‡, mesothelioma‡ |
| ***N-nitroso compounds*** | | |
| *N*-Nitrosodimethylamine | Polymers; batteries; nematocide (no longer in use) | Liver, lung, kidney |
| 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone | Research tool; cigarette smoke | Lung, liver |
| ***Olefines*** | | |
| Ethylene oxide | Glycol and polyester production; sterilization | Leukaemia‡, lymphoma‡ |
| Vinyl chloride (VC) | Plastics (PVC); co-polymers | Liver (angiosarcoma)‡ |
| Trichloroethylene | Degreasing operations; adhesives; lubricants | Liver‡, kidney‡§ |
| ***Paraffines/ethers*** | | |
| 1,2-Dichloroethane | VC production; solvent; degreaser (no longer in use) | Liver, lung, breast |
| Bis(chloromethyl)ether | Technical applications (rarely used) | Lung‡ |
| Mustard gas (sulphur mustard) | Chemical warfare in First World War; research | Lung‡ |
| Nitrogen mustard | Limited application as antineoplastic agent | Lung, skin, lymphoma |

*According to the National Toxicology Program 10th Report on Carcinogens, the compounds listed are known to be human carcinogens or reasonably anticipated to be human carcinogens[28]. This assessment is based on sufficent evidence of carcinogenicity in humans ('known') or animal models ('anticipated'). ‡Tumour sites observed in humans. §Limited evidence in humans. PVC, poly VC.

Luch 2005. Nature Rev Cancer 5: 113-25

National Toxicology Program. https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html

# Clasificación IARC

International Agency for Research on Cancer

World Health Organization

| Category | Description | Human Evidence | Animal Evidence |
|---|---|---|---|
| 1 | carcinogenic to humans | sufficient | none, inadequate, limited or sufficient |
| 2A | probably | limited | sufficient |
| 2B | possibly | none or inadequate | sufficient |
| 3 | not classifiable | none or inadequate | inadequate or limited |
| 4 | probably not carcinogenic | suggests not carcinogenic | suggests not carcinogenic |

www.iarc.fr

# Mecanismos Básicos

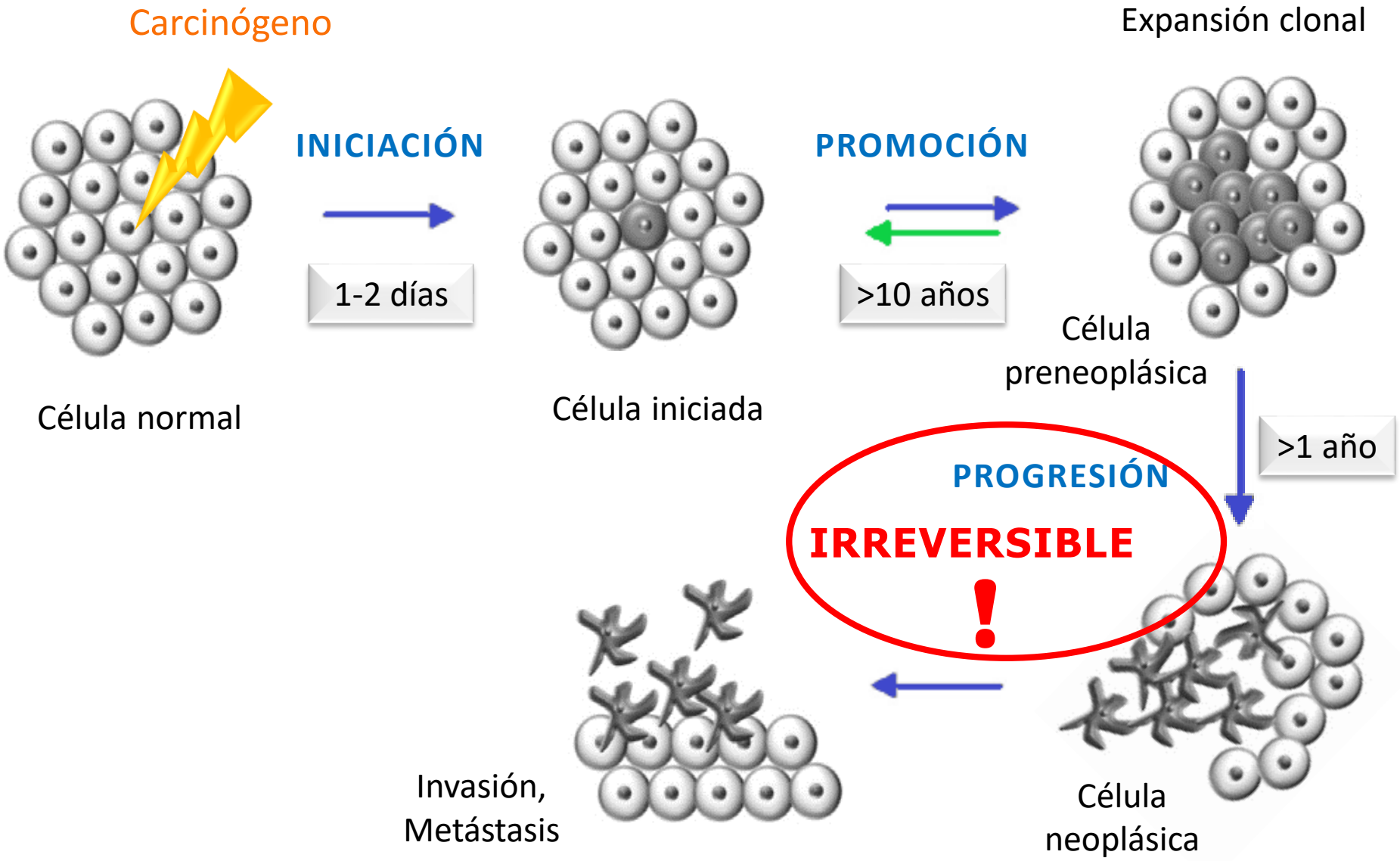

Vías de entrada:

- Difusión cutánea; Inhalación; Ingestión

Etapas:

- Iniciación (daño al ADN, **evento genético**)
- Promoción (condiciones que promueven proliferación, como factores de crecimiento, cambios epigenéticos. Crecimiento clonal)
- Progresión (acumulación de alteraciones genéticas, cambios epigenéticos, diversificación clonal)

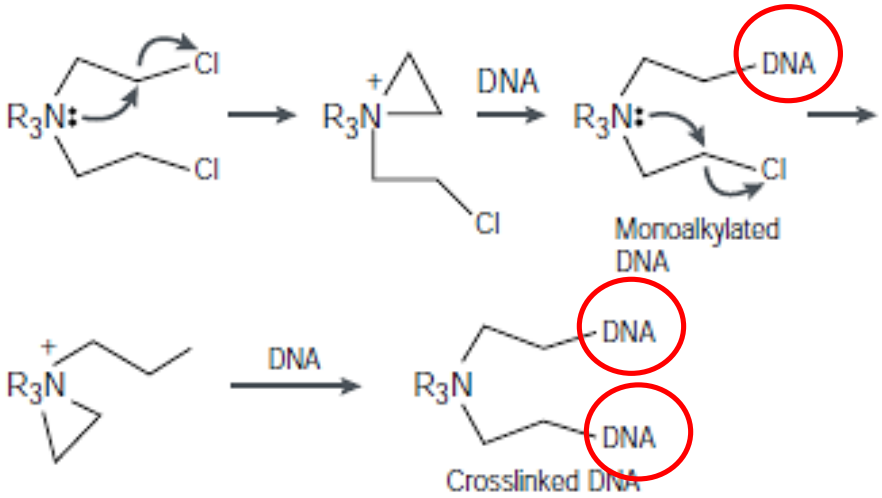
# Mecanismos Básicos: Etapas

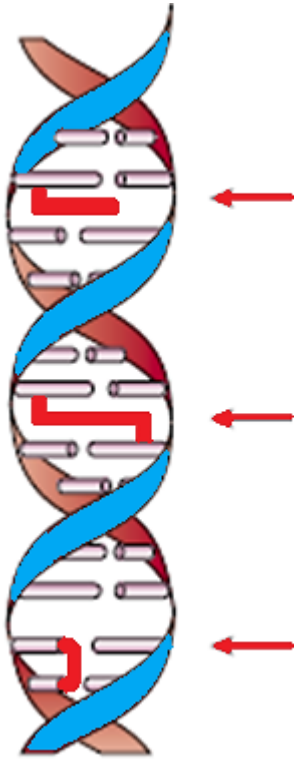


# Acción de Agentes Carcinogénicos

Algunos carcinógenos químicos actúan directamente sobre el ADN:

Ej: agentes alquilantes



Monoalkylated

Crosslinked (interstrand)

Melphalan, Chlorambucil

Crosslinked (intrastrand)

Cisplatino

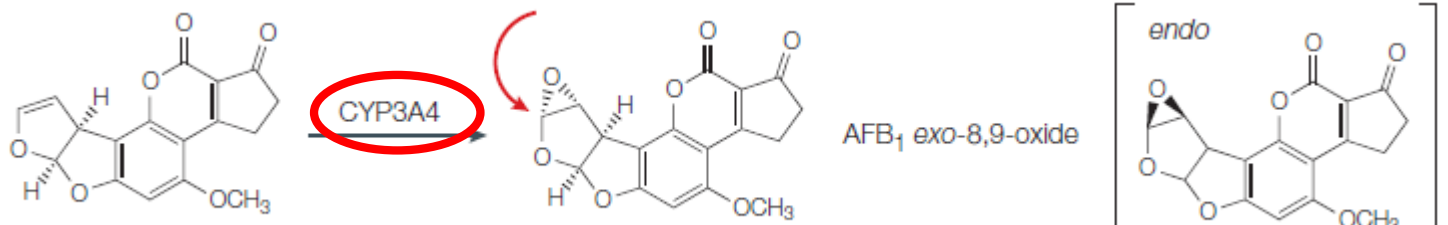
Hurley 2002. Nature Rev Cancer 2: 188-200

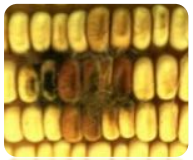
# Acción de Agentes Carcinogénicos

Muchos carcinógenos químicos requieren una activación metabólica previa:

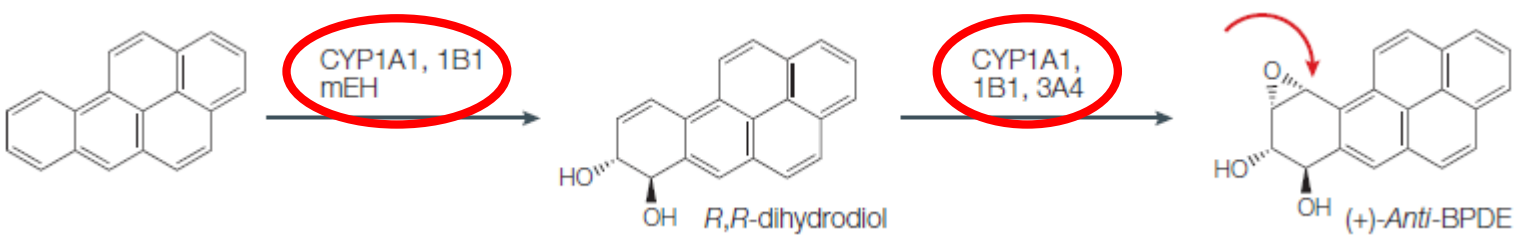
Pro-carcinógeno → Carcinógeno

Aflatoxina 1 (AFB1)



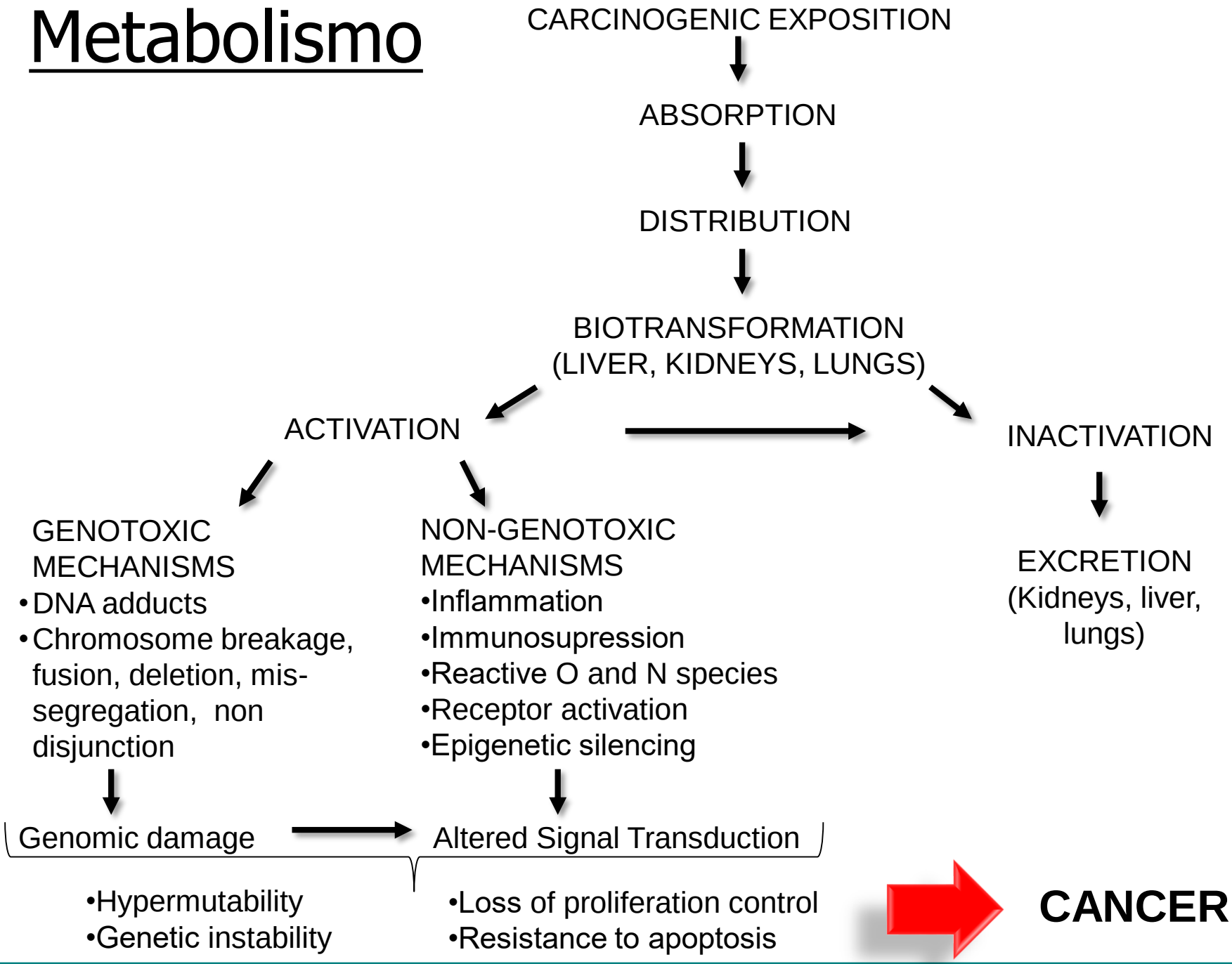



Benzo[a]pireno




Luch 2005. Nature Rev Cancer 5: 113-25

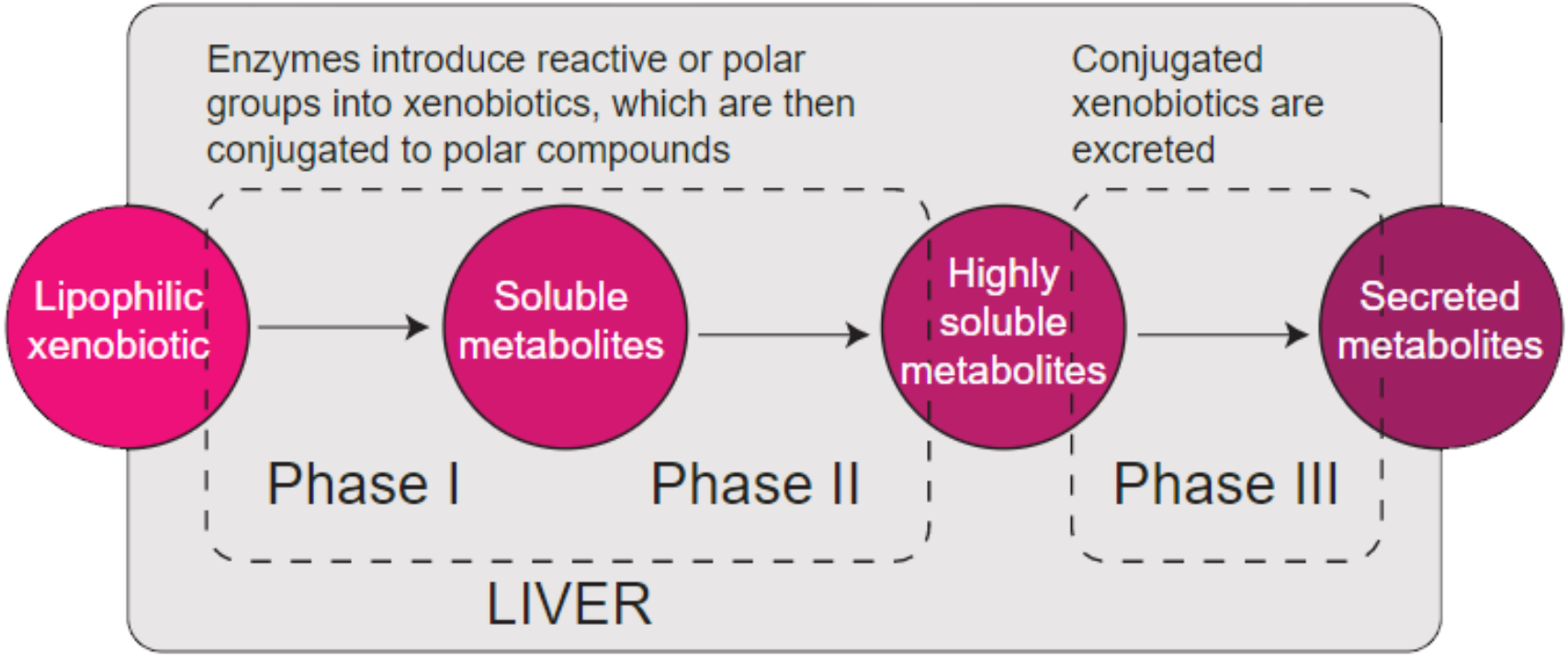
# Metabolismo




Oliveira 2007. Anais da Academia Brasileira de Ciências 79: 593-616

# Fases del Metabolismo

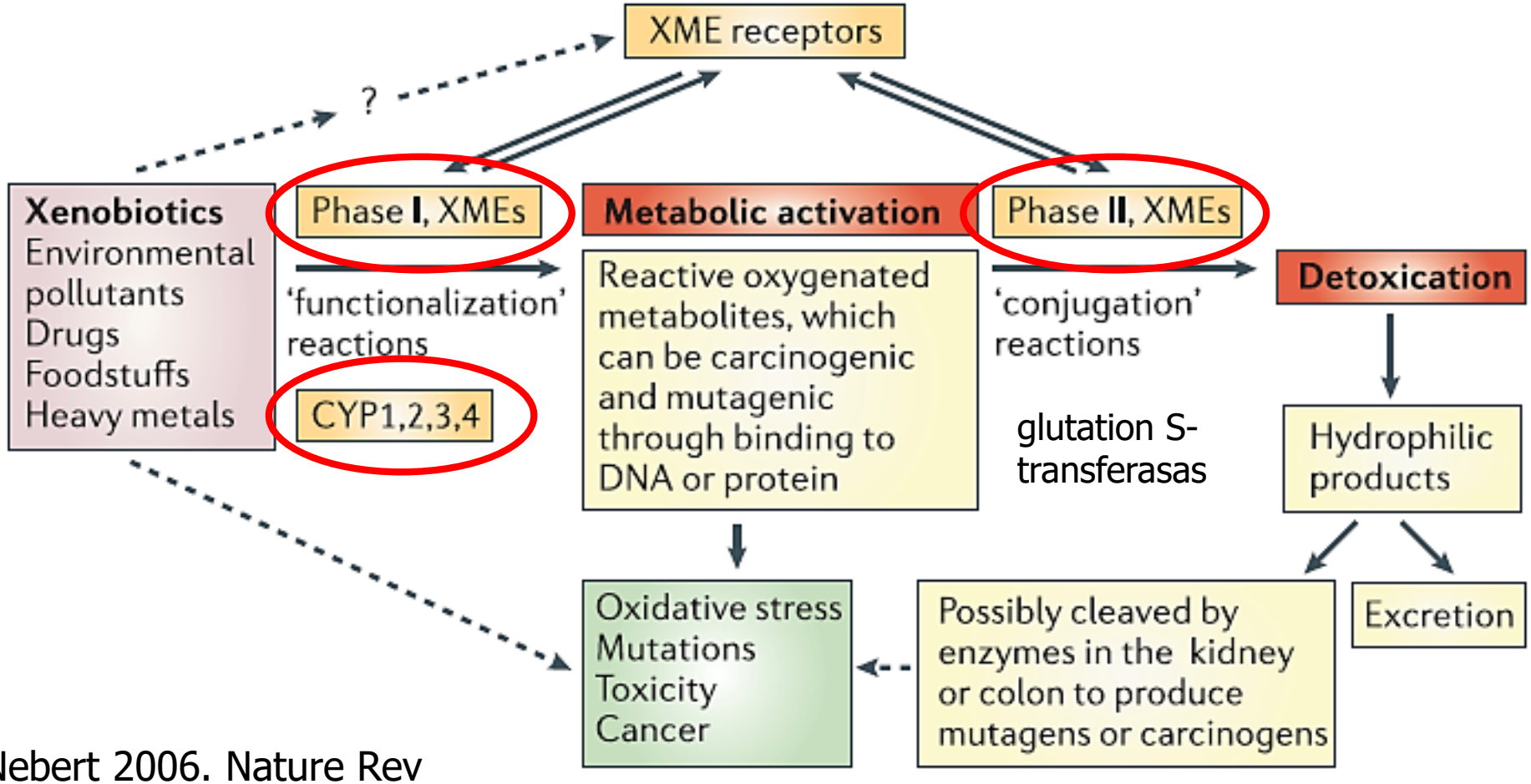
**Xenobiótico:** compuesto químico que no forma parte de un organismo vivo




https://www.youtube.com/watch?v=lDq48HQoIu8

# Fases del Metabolismo

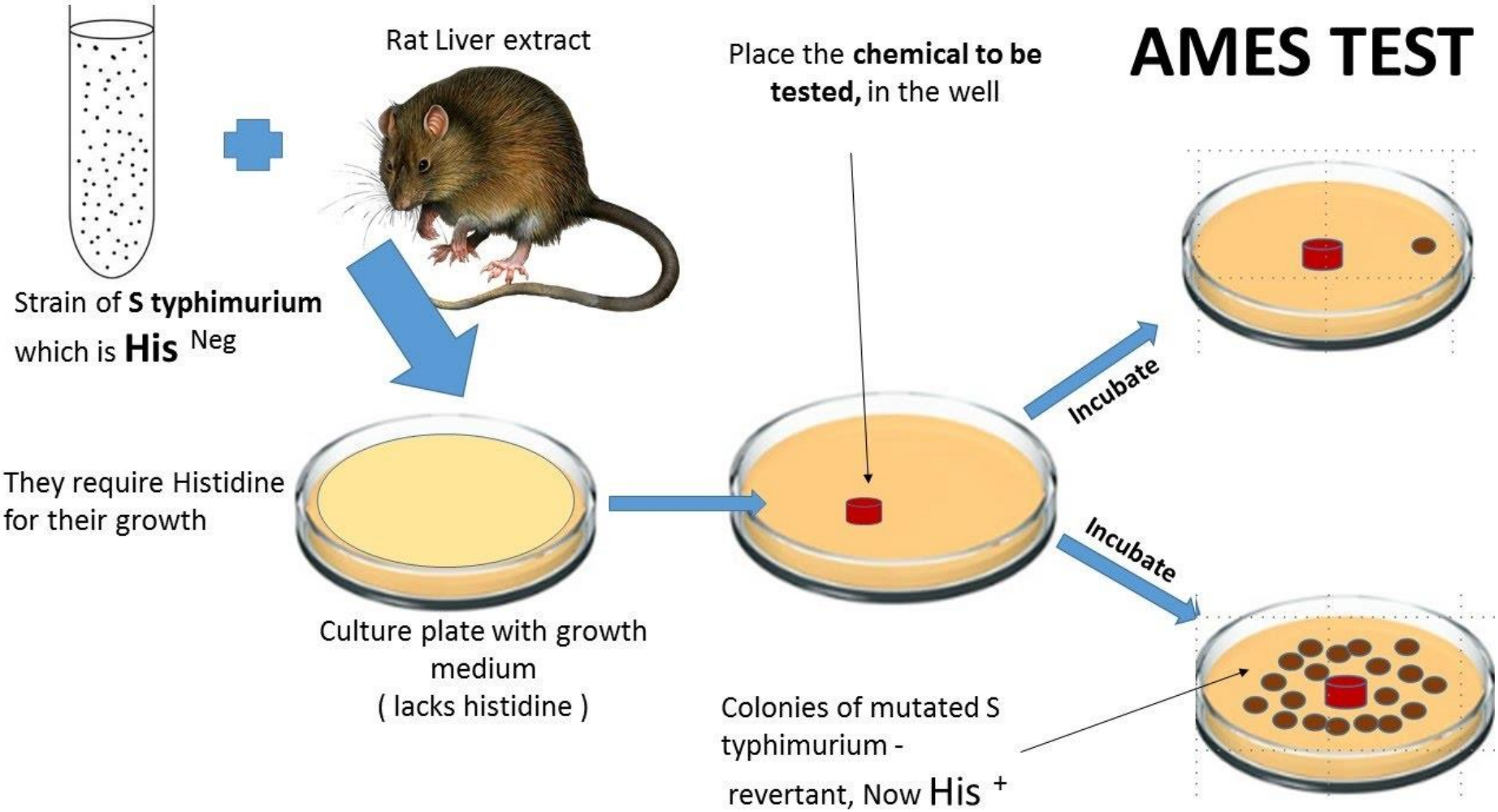
**Objetivo:** Metabolizar sustancia ajena para su eliminación del cuerpo




Nebert 2006. Nature Rev Cancer 6:947-60

# Determinación de Genotoxicidad

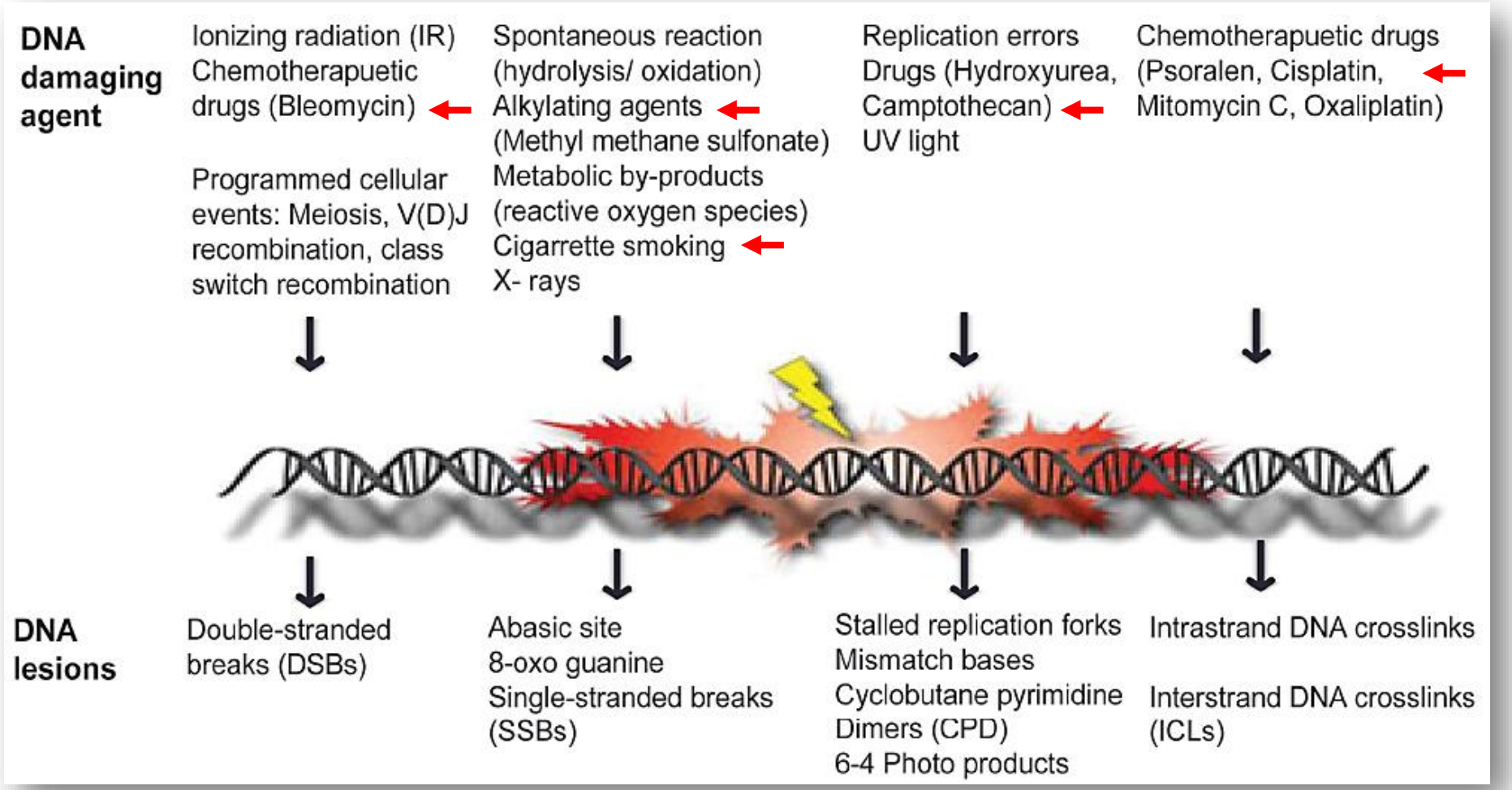
- Test de Ames



# MECANISMOS

# Agentes Causantes de Daño al ADN

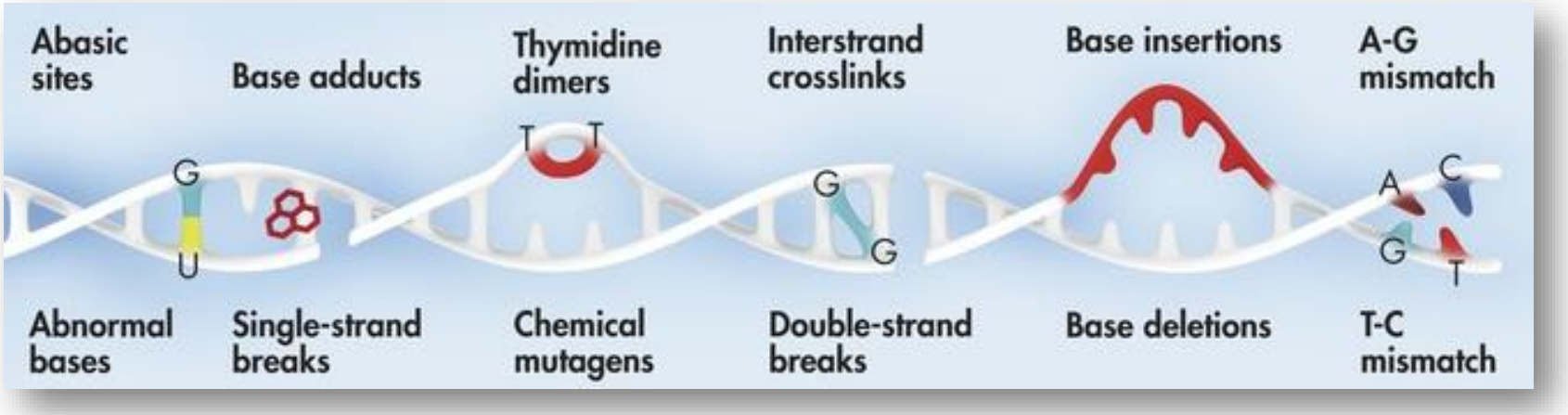
- Externos e internos




Ghosal 2013. Translational Cancer Res. doi: 10.3978/j.issn.2218-676X.2013.04.01

# Sistemas de reparación

- Definidos por el tipo de daño




**Base-excision repair (BER)**

**Nucleotide-excision repair (NER)**

**Recombination repair (HR, EJ)**

**Missmatch repair**

https://www.youtube.com/watch?v=vP8-5Bhd2ag

# Carcinógenos que Dañan el ADN

Table 2 | **Carcinogenic chemicals that form DNA adducts in humans**

| Chemical | Source | Cancer type | References |
|---|---|---|---|
| Aflatoxin $B_1$ | Mouldy food | Liver cancer | 10,11,50,51 |
| Aristolochic acid | Chinese herbs | Kidney cancer | 31,32 |
| 4-Aminobiphenyl | Dye/rubber manufacture; tobacco smoke | Bladder cancer | 33–37 |
| Benzidine | Dye manufacture | Bladder cancer | 37,38 |
| Benzo[*a*]pyrene (and other PAHs) | Tobacco smoke; ambient pollution; industrial waste | Lung cancer | 39–41 |
| Butadiene | Manufacture of resins, plastics, synthetic rubber | Leukaemia | 42,43 |
| MOCA | Chemical/dye manufacture | Lung and bladder cancer | 37,44 |
| NNK and NNN | Tobacco smoke; smokeless tobacco | Lung and head and neck cancer | 39,45,46 |
| Procarbazine and dacarbazine | Chemotherapeutic drugs | Leukaemia | 47–49 |
| Vinyl chloride | Polyvinylchloride manufacture | Liver cancer and angiosarcoma | 12,37 |

MOCA, 4,4′-methylene-bis-(2-chloroaniline); NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N′-nitrosonornicotine; PAH, polycyclic aromatic hydrocarbon.

Poirier 2004. Nature Rev Cancer 4:630-37.

¿Y si los genes involucrados en la reparación del ADN fallan?

# Genes involucrados en reparación del ADN

**Base excision repair (BER) (10 of 20 genes)**

DNA glycosylases
- OGG1*
- NEIL1*
- MUTYH
- UNG

PARP1

AP endonuclease
- APEX1
- APEX2*

DNA POL β

XRCC1

DNA ligase3

**Nucleotide excision repair (NER) (10 of 29 genes)**

**Global Genomic**

RAD23B*

TFIIH
- XPD helicase
- XPB ATPase

RPA

ERCC1*

XPF*

**Transcription Coupled**

CSA, CSB

ERCC1*

XPF*

XPG

XAB2

**Recombinational repair (HR/NHEJ)**

**Homologous Recombinational (10 of 21 genes)**

ATM*

NBN*

BRCA1*, BRCA2

RAD51*

RAD52*

P53

WRN*

BLM

FANCB*

**Non-homologous End Joining (3 of 7 genes)**

KU70, KU80

DNA-PKcs

**Mismatch repair (MMR) (10 genes)**

MLH1*

MLH3

MSH2*

MSH3

MSH4*

MSH5

MSH6*

PMS1

PMS2*

PMS2L3

(Rojo = genes bajo control epigenético
* = expresión alterada en cáncer)

# Fenotipos de Inestabilidad del Genoma

- Los defectos en diferentes mecanismos de reparación del ADN se asocian a manifestaciones fenotípicas características

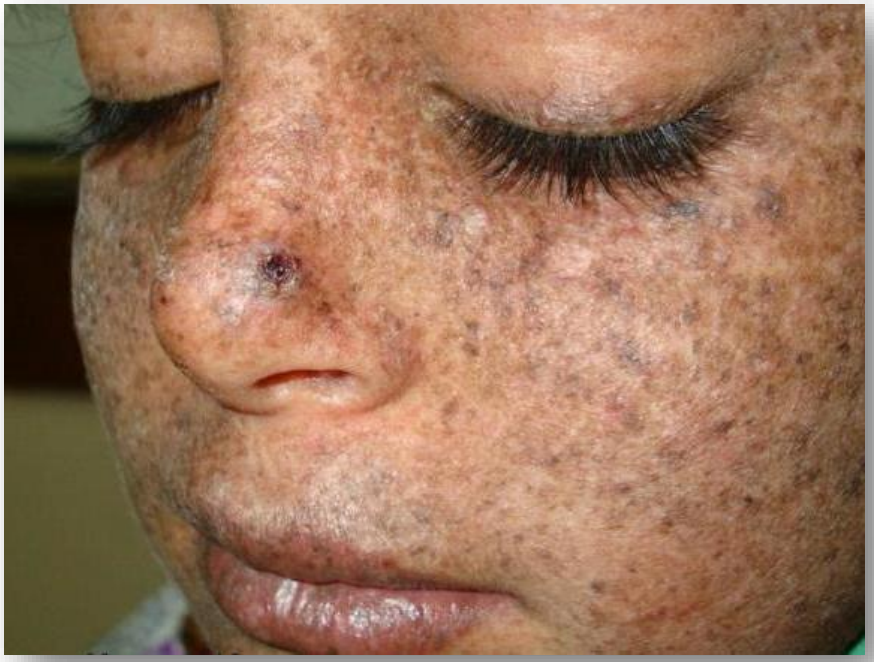
Ej: síndromes hereditarios

**Table 5–2 Some Inherited Syndromes with Defects in DNA Repair**

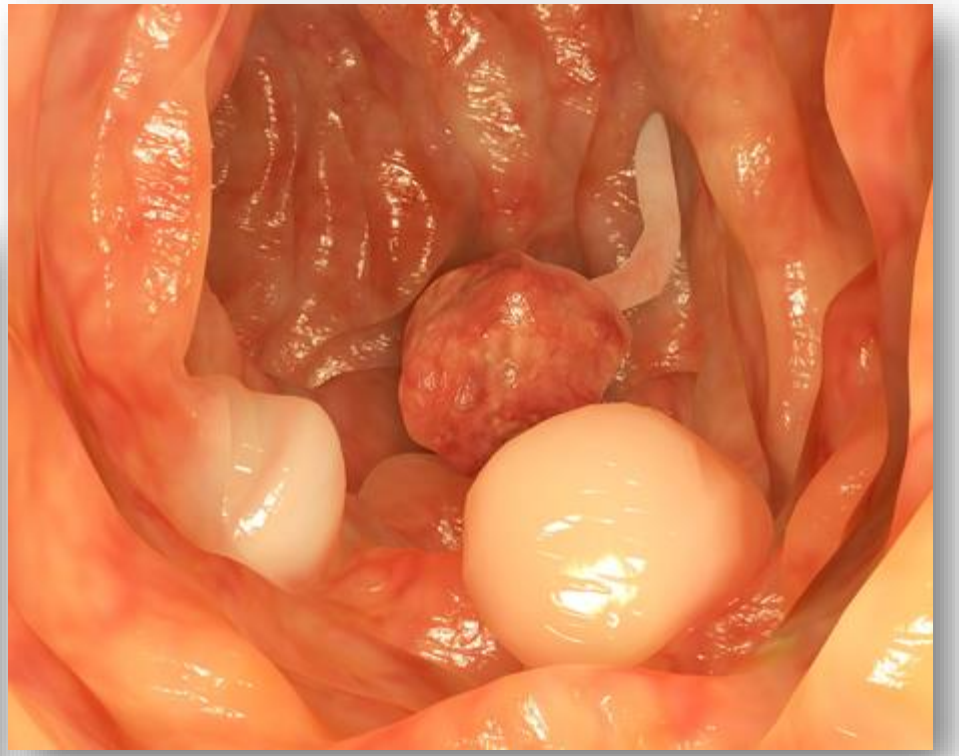
| NAME | PHENOTYPE | ENZYME OR PROCESS AFFECTED |
|---|---|---|
| MSH2, 3, 6, MLH1, PMS2 | colon cancer | mismatch repair |
| Xeroderma pigmentosum (XP) groups A–G | skin cancer, UV sensitivity, neurological abnormalities | nucleotide excision–repair |
| XP variant | UV sensitivity, skin cancer | translesion synthesis by DNA polymerase η |
| Ataxia telangiectasia (AT) | leukemia, lymphoma, γ-ray sensitivity, genome instability | ATM protein, a protein kinase activated by double-strand breaks |
| BRCA2 | breast, ovarian, and prostate cancer | repair by homologous recombination |
| Werner syndrome | premature aging, cancer at several sites, genome instability | accessory 3′-exonuclease and DNA helicase |
| Bloom syndrome | cancer at several sites, stunted growth, genome instability | accessory DNA helicase for replication |
| Fanconi anemia groups A–G | congenital abnormalities, leukemia, genome instability | DNA interstrand cross-link repair |
| 46 BR patient | hypersensitivity to DNA-damaging agents, genome instability | DNA ligase I |

# Fallas en la Reparación del ADN

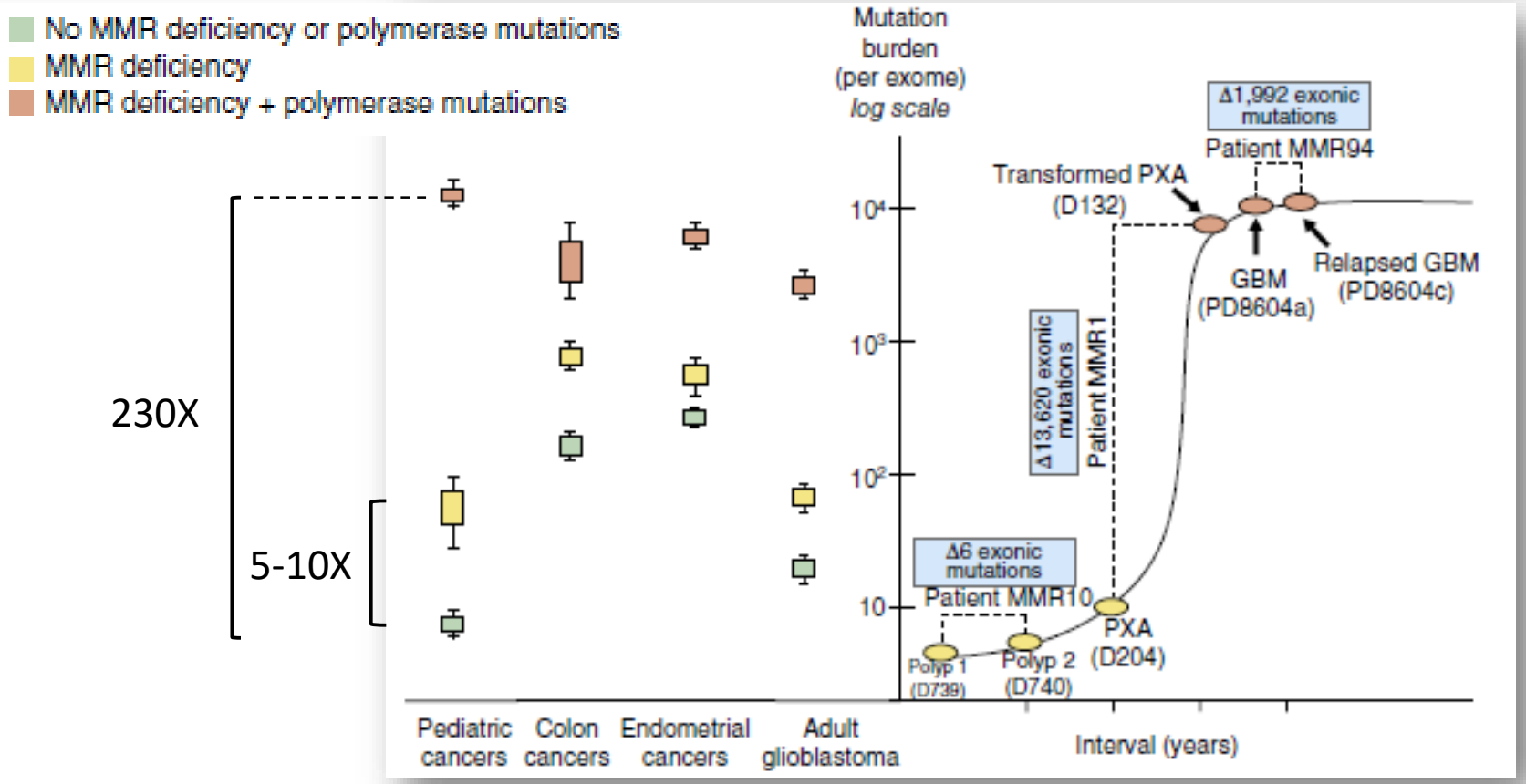
XP



Síndrome de Lynch



# Combined hereditary and somatic mutations of replication error repair genes result in rapid onset of ultra-hypermutated cancers

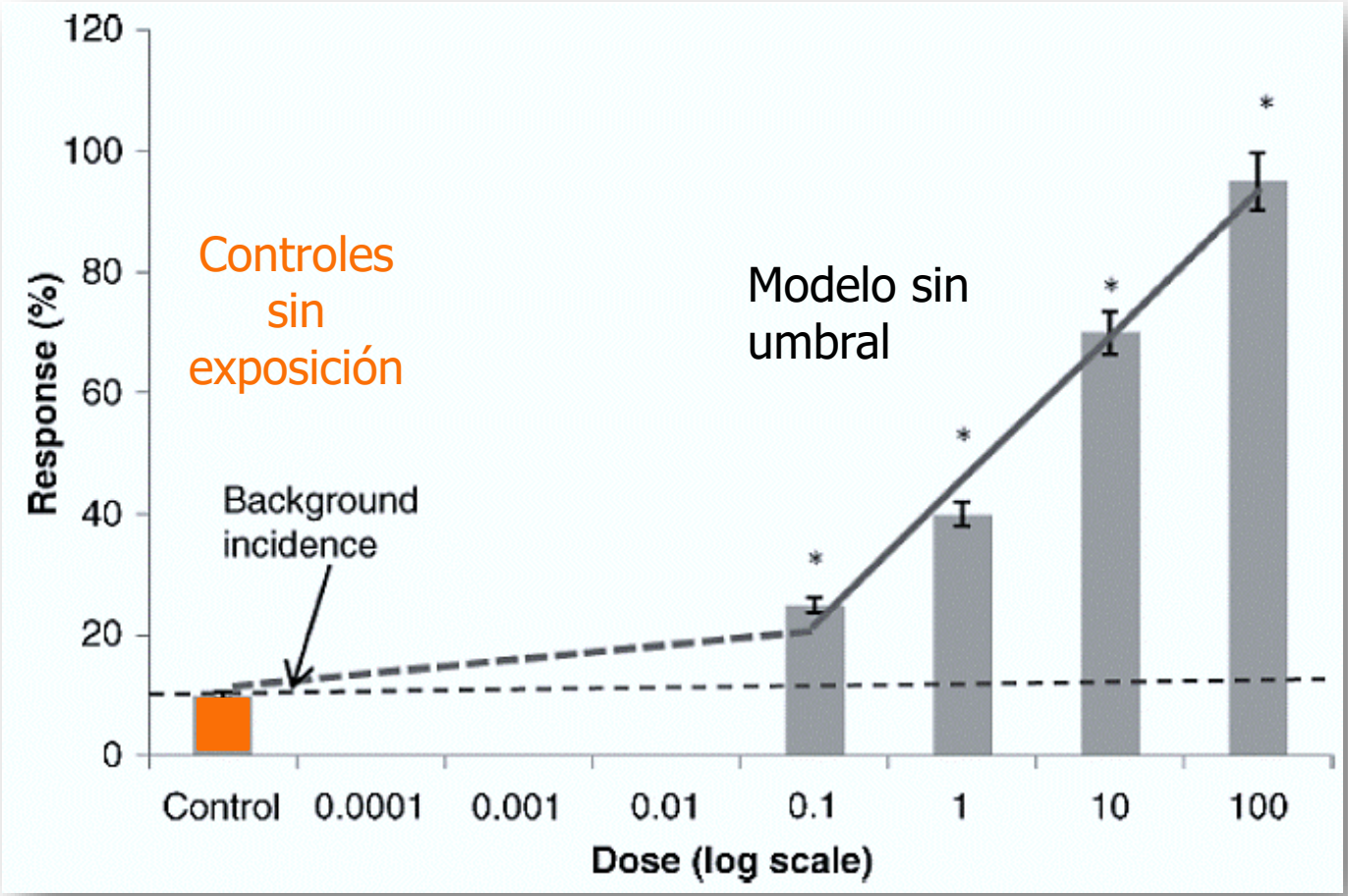



Nature Genetics (2015) doi:10.1038/ng.3202

¿Qué factores influyen en la susceptibilidad a agentes carcinogénicos?

# Factores Externos

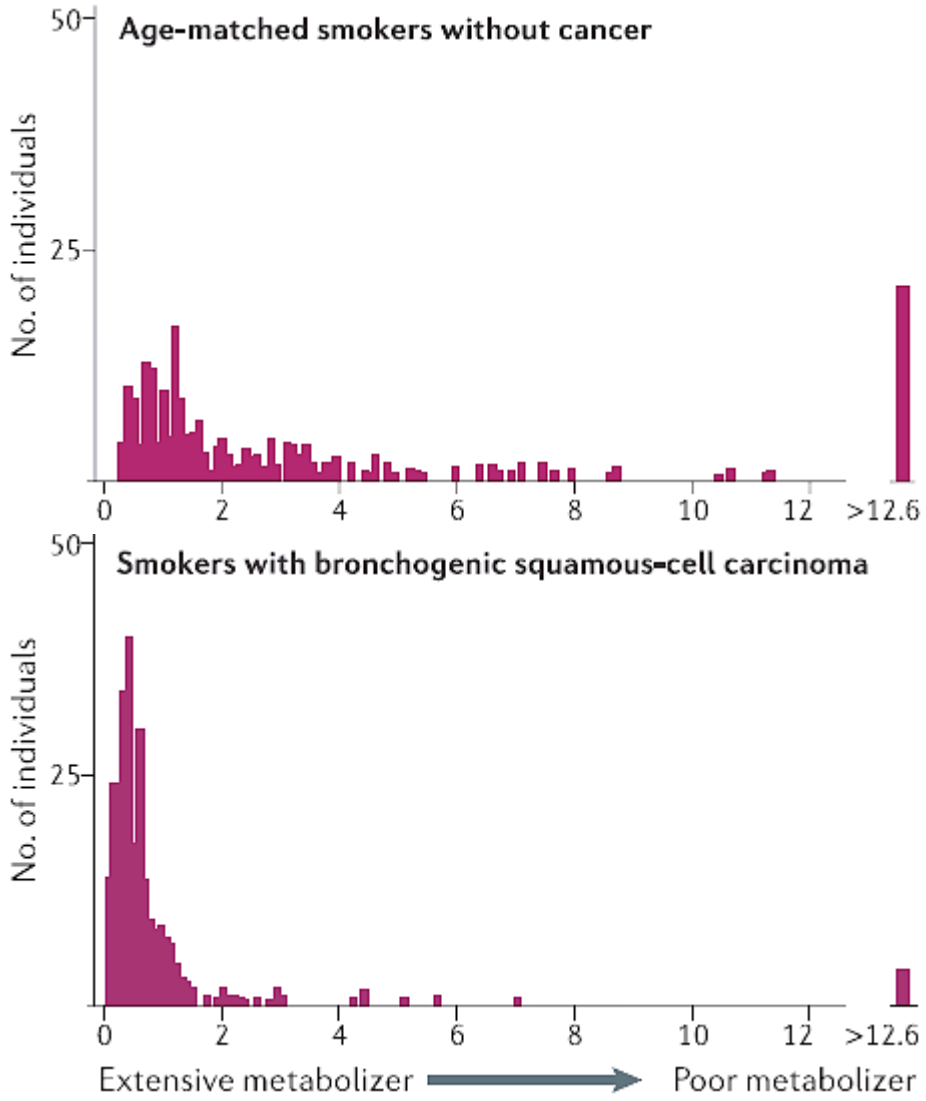
- Dosis
- Tiempo de exposición




Martin 2012. DOI: 10.1002/9781119950127.ch1

# Factores Internos

- Variantes génicas: enzimas familia citocromo P450




- Fumadores
- Con y sin cáncer pulmón
- Variación en eficiencia metabólica a través de CYP2D6

Nebert 2006. Nature Rev Cancer 6:947-60

¿La Epigenética es importante en la carinogénesis química?

# Ejemplo: Carcinogénesis por PAHs

**PAHs**
Exposición

**SUSCEPTIBILIDAD GENÉTICA**

Metabolismo
- APEX1
- CYP1A1
- GST family
- mEH
- NAT2

Reparación
- XPA
- XPC

**GENES**
Daño al ADN

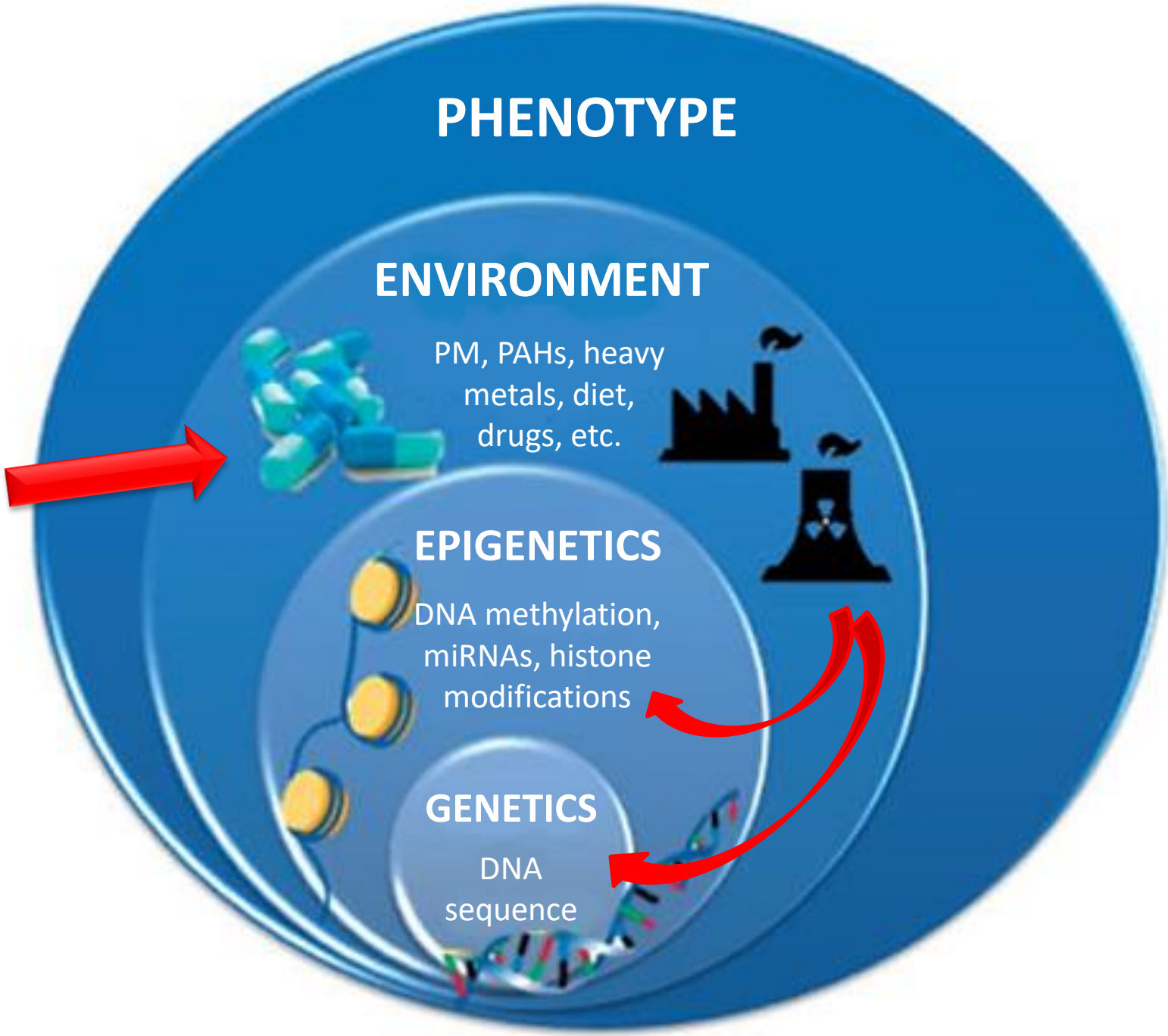
**PAHs**
TOXICIDAD

**FACTORES EPIGENÉTICOS**

**DNA Methylation**
- FOXP3
- $p14^{ARF}$
- $p15^{INK4b}$
- $p16^{INK4a}$

**miRNA signature**
- miR-638
- miR-181 family
- miR-24-3p, miR-1, miR -27a-3p, miR-28-5p, miR-142-5p, miR-150-5p

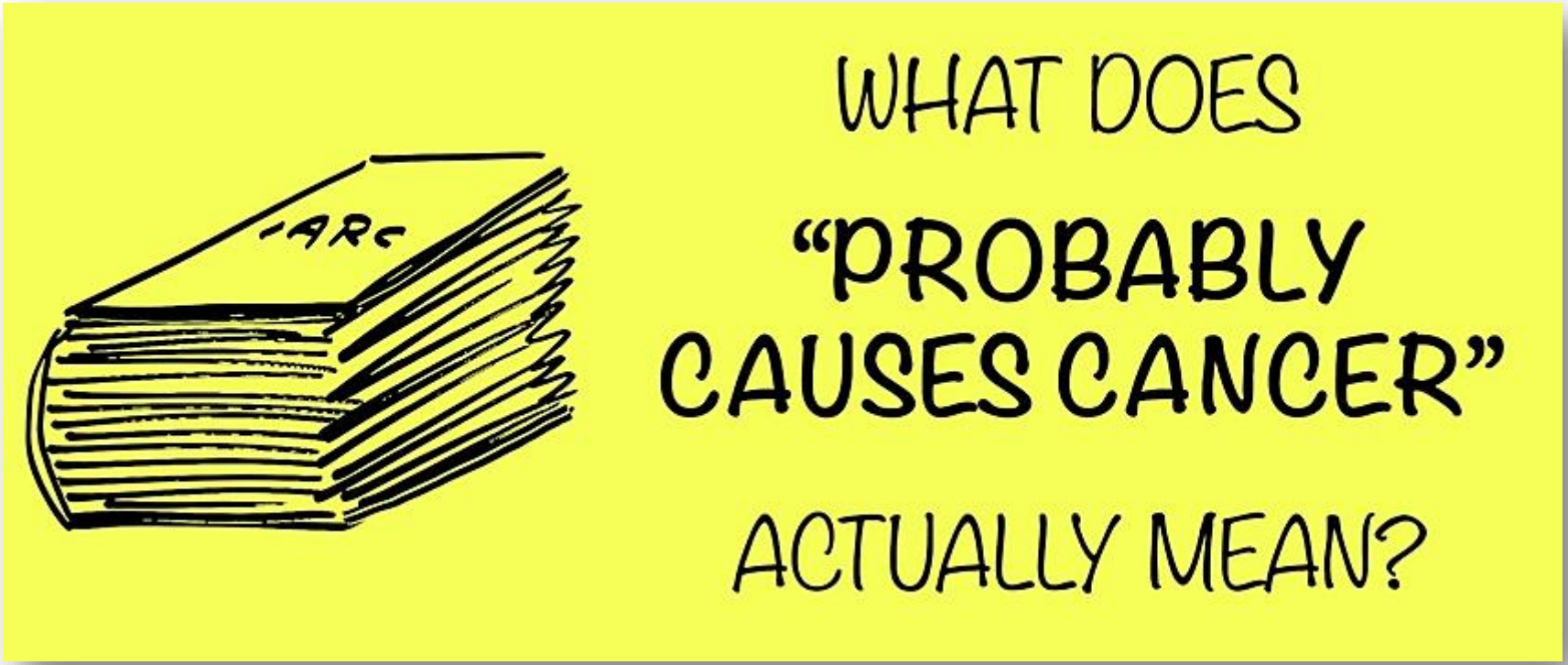
Ravegnini 2015. Toxicol Sciences 148: 2–13




Ravegnini 2015. Toxicol Sciences 148: 2–13

# Sustancias (aun) No-Reguladas

- Existe evidencia científica sugestiva
- No es suficiente para clasificación de riesgo como carcinógeno químico



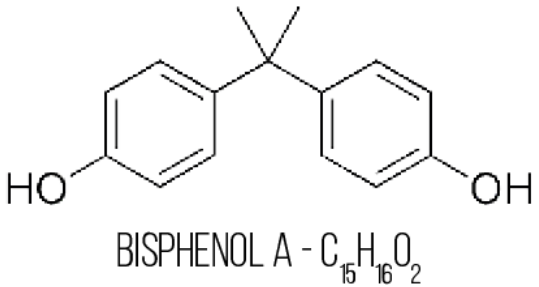
# Ejemplo: BPA

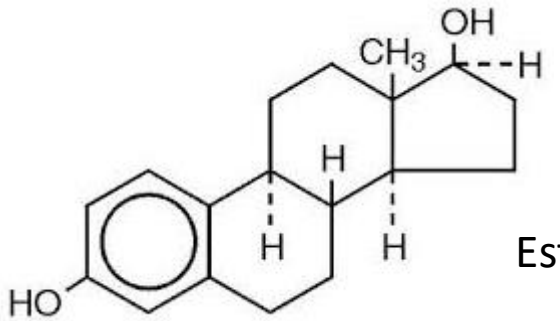
*Reprod Toxicol*. 2016 January ; 59: 167–182. doi:10.1016/j.reprotox.2015.09.006.

## A Review of the Carcinogenic Potential of Bisphenol A

**Darcie D Seachrist[1,#], Kristen W. Bonk[1,#], Shuk-Mei Ho[2], Gail S. Prins[3], Ana M. Soto[4], and Ruth A. Keri[1,*]**

Ruth A. Keri: keri@case.edu




Estrógenos

# Legislación

## Food Additive Regulations Amended to No Longer Provide for the Use of BPA-Based Materials in Baby Bottles, Sippy Cups, and Infant Formula Packaging

- **FDA has amended its regulations to no longer provide for the use of BPA-based polycarbonate resins in baby bottles and sippy cups.** In July, 2012, FDA took this action in response to a food additive petition filed by the American Chemistry Council (ACC) [9]. The ACC petition demonstrated, from publicly available information and information collected from industry sources, that the use of polycarbonate resins in baby bottles and sippy cups had been abandoned.
- **FDA has amended its regulations to no longer provide for the use of BPA-based epoxy resins as coatings in packaging for infant formula.** In July, 2013, FDA took this action in response to a food additive petition filed by Congressman Edward Markey [10] of Massachusetts. This petition demonstrated, from publicly available information and information collected from industry sources, that the use of BPA-based epoxy resins as coatings in packaging for infant formula had been abandoned.

# Resumen

- Evidencia se originó por estudios epidemiológicos y de individuos expuestos a agentes mutagénicos
- Las sustancias carcinogénicas actúan directamente o a través de activación metabólica
- Involucra un daño irreversible al ADN (iniciación) como primer evento
- La susceptibilidad hacia carcinógenos puede variar entre individuos: factores internos, dosis, tiempo de exposición

# Bibliografía


- **The Biology of Cancer**. Robert Weinberg
- **Holland-Frei Cancer Medicine**, 6th Edition. Chapter 17 (https://www.ncbi.nlm.nih.gov/books/NBK13216/)
- Artículos citados en la clase.