GENOTOXICITY ASSESSMENT – WHEN YOU NEED IT AND HOW TO DO THE EVALUATION

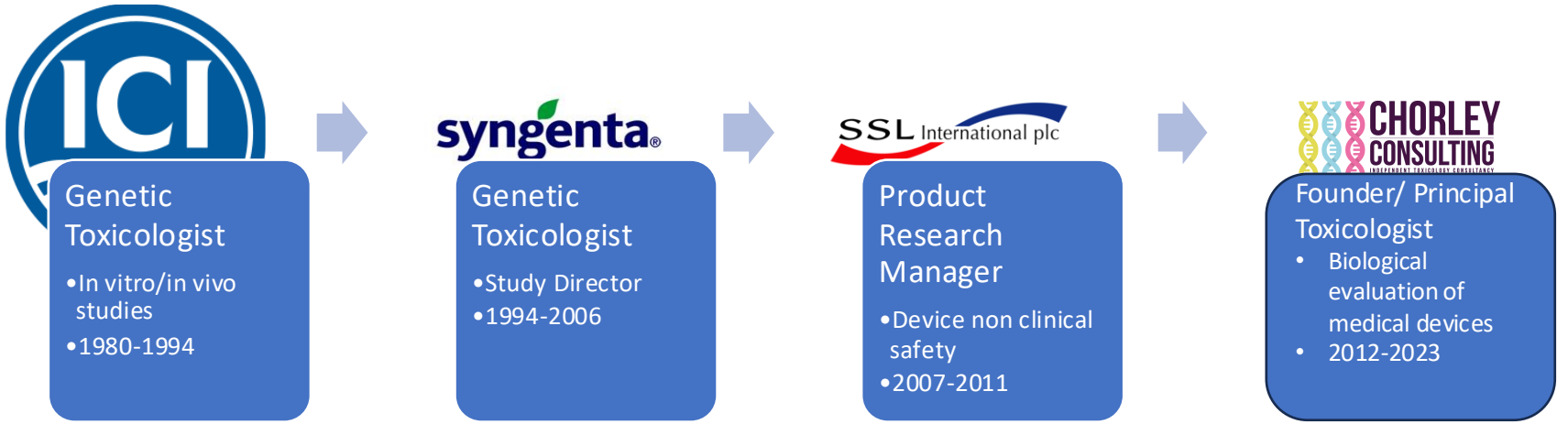
PART 1 – GENOTOXICITY AND CARCINOGENICITY

Philip Clay, Principal Toxicologist
Chorley Consulting Ltd.

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INTRODUCTIONS

- Philip Clay, UK/ERT;
  - Toxicologist with Chorley Consulting



- Introductions from delegates
  - Background/experience with genetic toxicology

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TODAY

- Part 1
  - What is cancer?
  - What is genotoxicity?
  - What is the relationship between the two?
- Part 2
  - How do I evaluate genotoxicity?



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CANCER VS GENOTOXICITY

- Cancer is a multi-step proc…on, promotion and progression.
- Chemical carcinogens can …es to induce their carcinogenic effects.
- In the majority of instances, chemical carcinogens, directly or after metabolism, induce DNA damage and act in a 'genotoxic' manner.
- There is, however, a group of carcinogens that induce cancer via non-genotoxic mechanisms.

Genetic toxicology is the study of agents that can damage the DNA and chromosomes of cells.

Non-genotoxic carcinogens have been shown to act as:

- tumor promoters (1,4-dichlorobenzene)
- endocrine-modifiers (17beta-estradiol)
- receptor-mediators (2,3,7,8-tetrachlorodibenzo-p-dioxin)
- immunosuppressants (cyclosporine) or
- inducers of tissue-specific toxicity and inflammatory responses (metals such as arsenic and beryllium).

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CANCER, GENOTOXICITY AND MEDICAL DEVICES

- Medical devices may pose a risk of genotoxicity and/or cancer, either by chemicals leaching from the device, or by the presence of the device itself.
- The requirements and methods to assess such risk are specified primarily in ISO 10993-1 and ISO 10993-3

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ISO 10993-1

Biological evaluation of medical devices —

Part 1:
Requirements and general principles for the evaluation of biological safety within a risk management process

Sixth edition
2025-11

- Tells us <u>when</u> genotoxicity and/or carcinogenicity should be evaluated for our device

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ISO 10993/1
SECTION 6.5.7 GENOTOXICITY

- Genotoxicity evaluation is carried out to determine if constituents are present which can result in adverse effects related to genotoxicity. **Duration of contact is important in determining the need for a genotoxicity assessment.**
- Unless manufactured from novel materials or intended for use in certain sensitive populations, an **evaluation for genotoxicity is not usually required** for medical devices:
    - in contact with intact skin for any duration; or
    - in limited duration contact with tissues, other than implantable medical devices with circulating blood contact, or medical devices that are part of extracorporeal circuits.
- However, if other factors apply to the medical device, an evaluation for genotoxicity can be necessary.....

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ISO 10993/1
SECTION 6.5.7 GENOTOXICITY

- Evaluation for genotoxicity is required for medical devices in:
    - prolonged or long-term contact with all tissues (including circulating blood) except intact skin;
    - limited duration contact with circulating blood, if implantable or part of an extracorporeal circuit.

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ISO 10993/1
SECTION 6.5.7 GENOTOXICITY

Information from material supplier

Chemical analysis

- However, if the medical device contains constituents known to be genotoxic, the potential for relevant biological harms should assessment irrespective of the type or durati contained in ISO 10993-3.

Biological evaluation of medical devices

Part 18: Chemical characterization of medical device materials within a risk management process

- Genotoxicity can be evaluated in a toxicological risk assessment of chemical information.
- Any toxicological risk assessment shall be conducted in accordance with the requirements of ISO 10993-17 unless otherwise justified.

Biological evaluation of medical devices

Part 17: Toxicological risk assessment of medical device constituents

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ISO 10993/1
SECTION 6.5.8 CARCINOGENICITY

- Carcinogenicity can be of concern in medical devices resulting from:
  - genotoxic mechanisms such as exposure to genotoxic constituents; or
  - non-genotoxic mechanisms such as induction of cell proliferation or chronic inflammation
- Unless manufactured from novel materials or intended for use in certain sensitive populations, **evaluation for carcinogenicity is not usually required for medical devices in contact with intact skin**.
- However, if other factors (see 6.5.11) apply to the medical device, an evaluation for carcinogenicity can be necessary.

6.5.11.9 Presence of hazardous constituents

If material information indicates that one or more constituents with known toxicities are present in a medical device at levels that can be toxic, the biological evaluation shall address the associated biological risk, regardless of the categorization (see 6.3).

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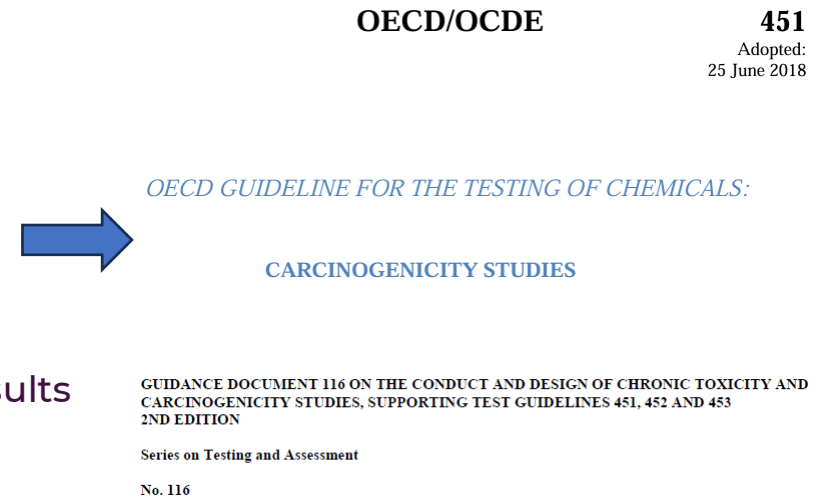
ISO 10993/1
SECTION 6.5.8 CARCINOGENICITY

- Medical devices in long term contact with any other tissues, including circulating blood shall be evaluated for carcinogenicity.
- *In vivo* carcinogenicity tests use a large number of animals and are usually of limited sensitivity and relevance to exposure from medical devices. In the absence of any significant cancer risk, it is rare for carcinogenicity tests to be considered appropriate for medical devices.

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CARCINOGENICITY TESTS - WHY NOT?

- Lifetime bioassays in rodents, or shorter term transgenic assays (e.g. mouse Ras H2A)
  - High costs
  - Large numbers of animals
  - Dose/exposure
  - Difficulty in interpreting results



OECD/OCDE 451

Adopted:
25 June 2018

OECD GUIDELINE FOR THE TESTING OF CHEMICALS:

CARCINOGENICITY STUDIES

GUIDANCE DOCUMENT 116 ON THE CONDUCT AND DESIGN OF CHRONIC TOXICITY AND CARCINOGENICITY STUDIES, SUPPORTING TEST GUIDELINES 451, 452 AND 453
2ND EDITION

Series on Testing and Assessment

No. 116

- 50 animals/dose/sex
- Exposure 100-150 x clinical exposure
  - Limited ability to exaggerate exposure with implants
  - Multiple vehicles for extracts
- Variable background tumour rates

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ISO 10993/1

SECTION 6.5.8 CARCINOGENICITY

- ……

- Chemical information and subsequent toxicological risk assessment can provide a basis for the evaluation of carcinogenicity. If the medical device contains constituents known to be carcinogenic, the potential for these harms should be considered in the biological risk assessment irrespective of the type or duration of body contact. Further information is contained in ISO 10993-3.

- Any toxicological risk assessment shall be conducted in accordance with the requirements of ISO 10993-17 unless otherwise justified.

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WHEN TO EVALUATE - ISO 10993/1

Table 1 — Biological effects for medical devices in contact with intact skin

Duration	Biological effect[a b c]							
	Cytotoxicity (6.5.2)	Sensitization (6.5.3)	Irritation (6.5.4)	Systemic toxicity (6.5.5)[d]	Local effects after tissue contact (6.5.6)	Genotoxicity (6.5.7)	Carcinogenicity (6.5.8)	Haemocompatibility (6.5.9)
A – limited (≤24 h)	E	E	E					
B – prolonged (>24 h to 30 d)	E	E	E					
C – long-term (>30 d)	E	E	E					

Table 2 — Biological effects for medical devices in contact with intact mucosal membranes

Duration	Biological effect[a b c]							
	Cytotoxicity (6.5.2)	Sensitization (6.5.3)	Irritation (6.5.4)	Systemic toxicity (6.5.5)[e]	Local effects after *tissue* contact (6.5.6)[d]	Genotoxicity (6.5.7)	Carcinogenicity (6.5.8)	Haemocompatibility (6.5.9)
A – limited (≤24 h)	E	E	E					
B – prolonged (>24 h to 30 d)	E	E	E	E	E	E		
C – long-term (>30 d)	E	E	E	E	E	E	E	

Table 3 — Biological effects for medical devices in contact with either breached or compromised surfaces (skin or mucosal membranes) or internal tissues other than circulating blood

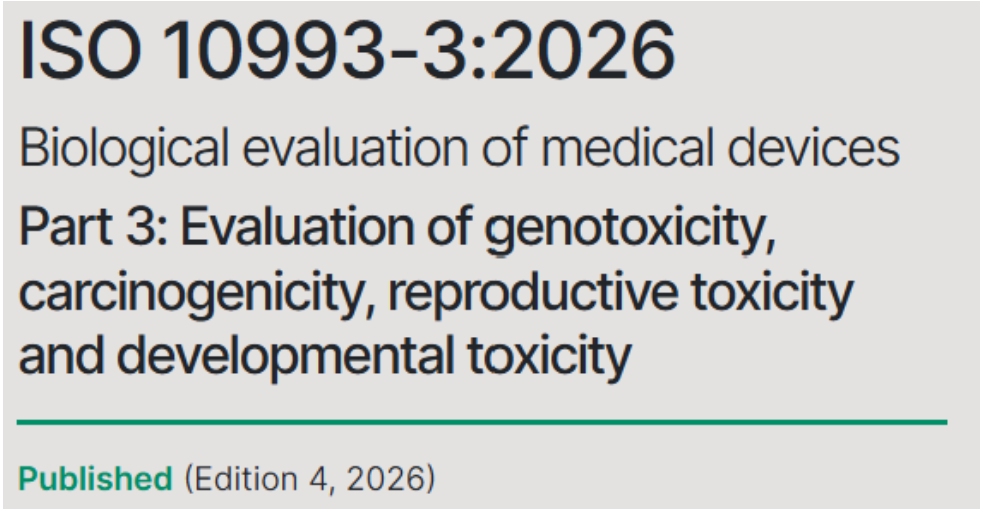
Duration	Biological effect[a b c]							
	Cytotoxicity (6.5.2)	Sensitization (6.5.3)	Irritation (6.5.4)	Systemic toxicity (6.5.5)[e]	Local effects after tissue contact (6.5.6)[d]	Genotoxicity (6.5.7)	Carcinogenicity (6.5.8)	Haemocompatibility (6.5.9)
A – limited (≤24 h)	E	E	E	E				
B – prolonged (>24 h to 30 d)	E	E	E	E	E	E		
C – long-term (>30 d)	E	E	E	E	E	E	E	

Table 4 — Biological effects for medical devices in contact with circulating blood

Duration	Biological effect[a b c]							
	Cytotoxicity (6.5.2)	Sensitization (6.5.3)	Irritation (6.5.4)	Systemic toxicity (6.5.5)[f]	Local effects after tissue contact (6.5.6)	Genotoxicity (6.5.7)	Carcinogenicity (6.5.8)	Haemocompatibility (6.5.9)
A – limited (≤24 h)	E	E	E	E		E[e]		E
B – prolonged (>24 h to 30 d)	E	E	E	E	E[d]	E		E
C – long-term (>30 d)	E	E	E	E	E[d]	E	E	E

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ISO 10993/3



- Tells us **how** genotoxicity and/or carcinogenicity should be evaluated for our device – to follow

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GENOTOXICITY VS CARCINOGENICITY

- Genotoxicity, mutagenicity, and carcinogenicity are related but distinct concepts.
- They are often confused because all three involve harmful effects at the cellular or genetic level, but each describes a different type of hazard.

This means that not all genotoxic substances are carcinogenic, and not all carcinogens are genotoxic

Genotoxicity is the ability to damage the genetic material in a cell. This damage can occur through different mechanisms, such as breaking DNA strands, changing chromosome structure or number, or interfering with the processes that copy or repair DNA. The changes may be inherited (mutations), but non-heritable genetic alterations are also possible

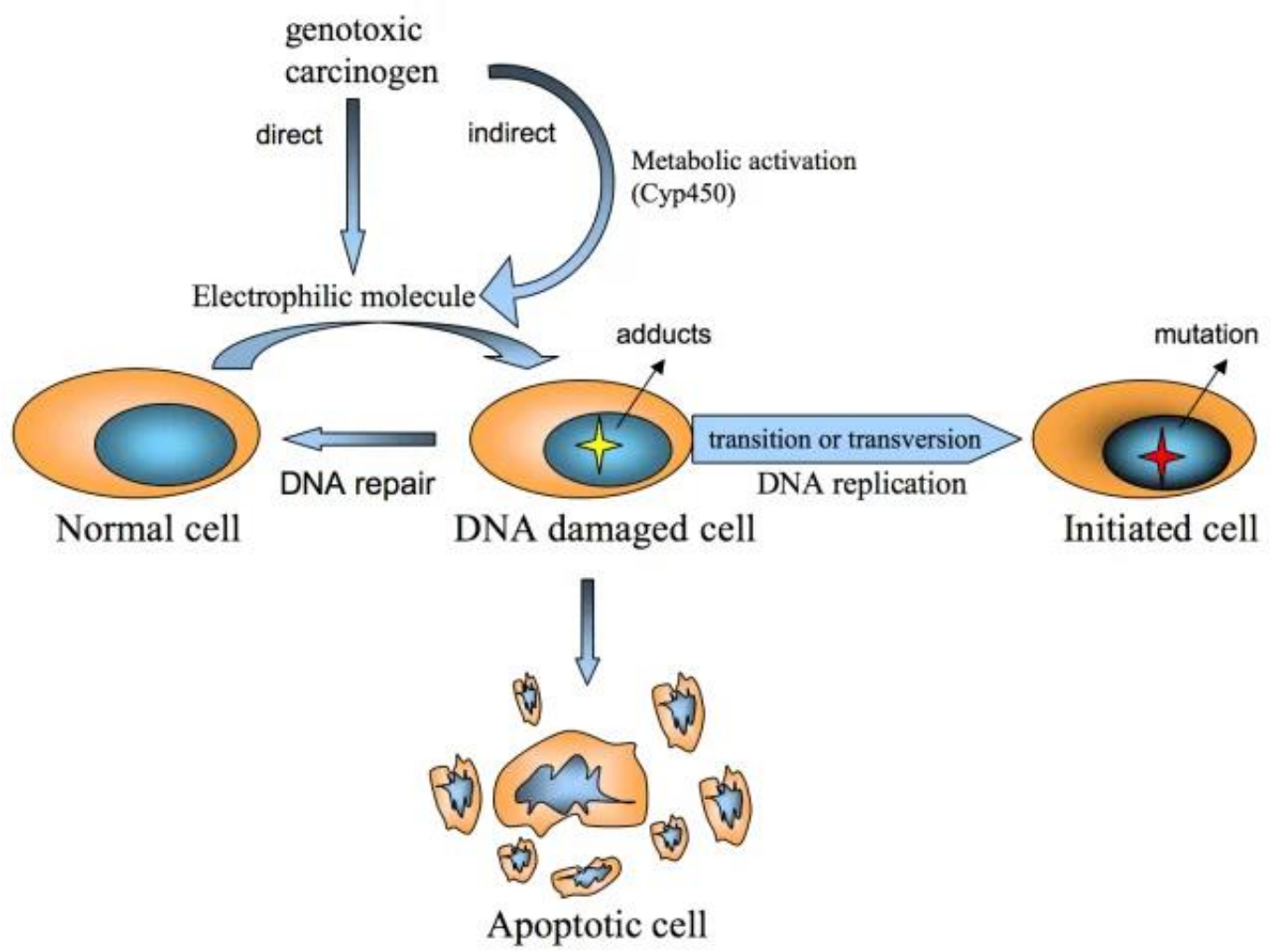
All mutagens are genotoxic, but not all genotoxic substances are mutagenic. Some may damage chromosomes without changing the DNA sequence itself

Carcinogenicity is the ability to cause cancer. Some carcinogens act through genotoxic mechanisms, while others cause cancer by different mechanisms such as chronic inflammation or hormonal disruption.

Mutagenicity is the ability to cause mutations, or permanent changes in the DNA sequence. It is a subset of genotoxicity.

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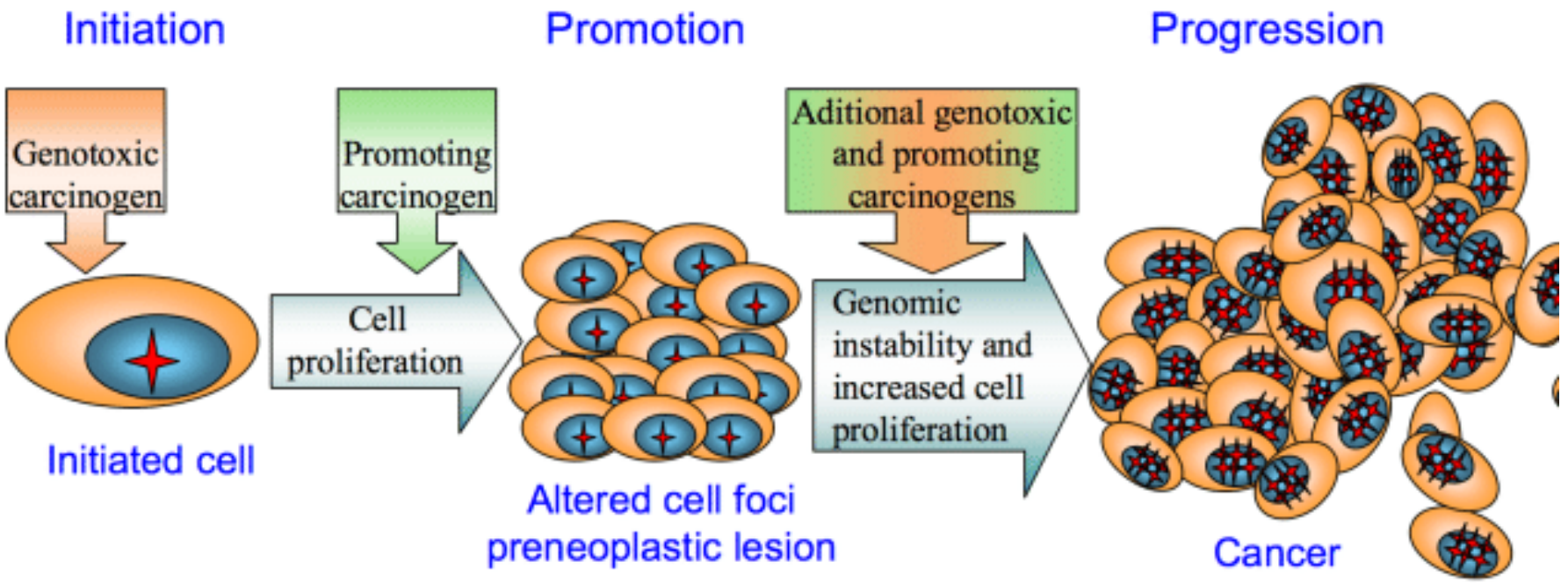
GENOTOXIC CARCINOGENICITY



Pérez-Carreón, Julio & Meléndez-Zajgla, Jorge. (2012). In vitro and in vivo models for cancer research. Molecular Oncology Principles and Recent Advances. 148-162. 10.2174/978160805016111201010148.

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GENOTOXIC CARCINOGENICITY

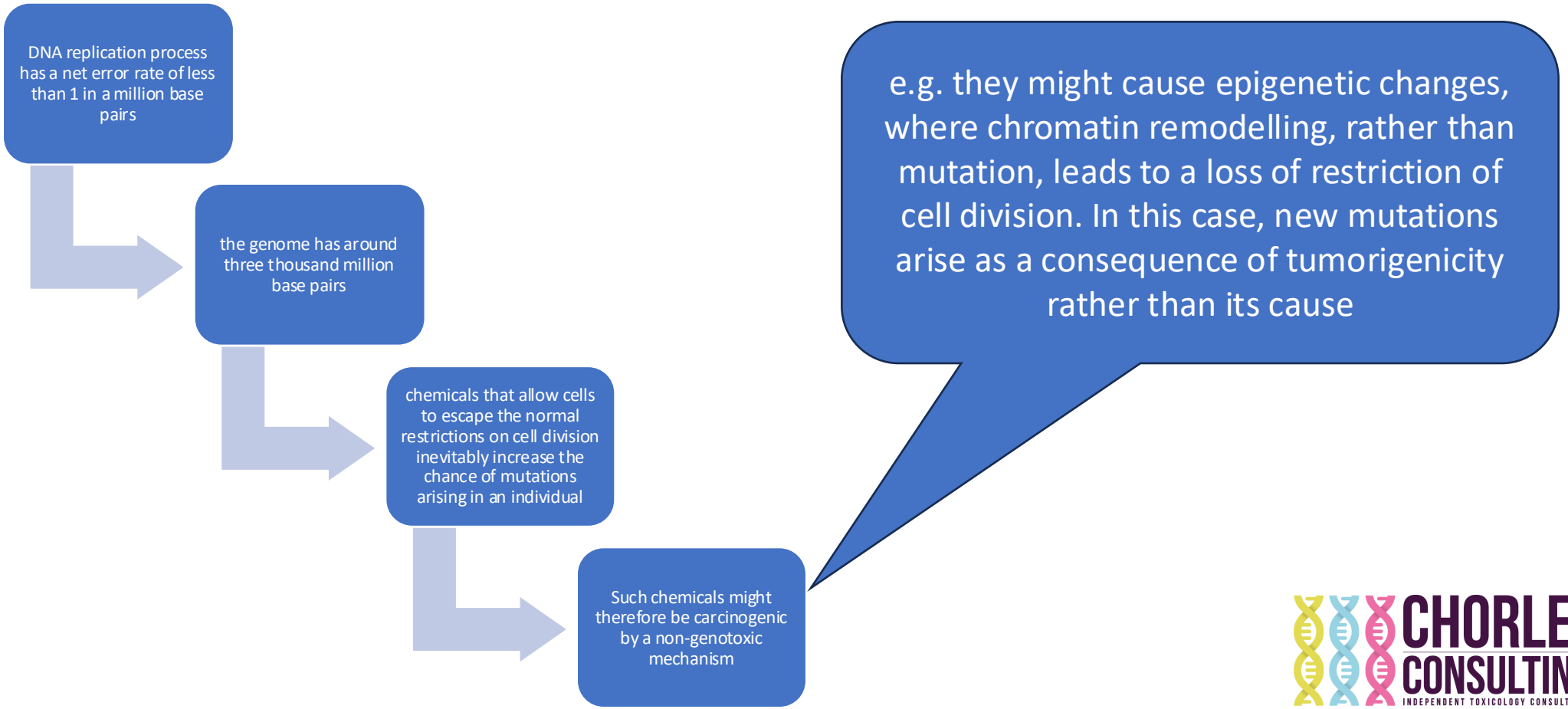


Pérez-Carreón, Julio & Meléndez-Zajgla, Jorge. (2012). In vitro and in vivo models for cancer research. Molecular Oncology Principles and Recent Advances. 148-162. 10.2174/978160805016111201010148.

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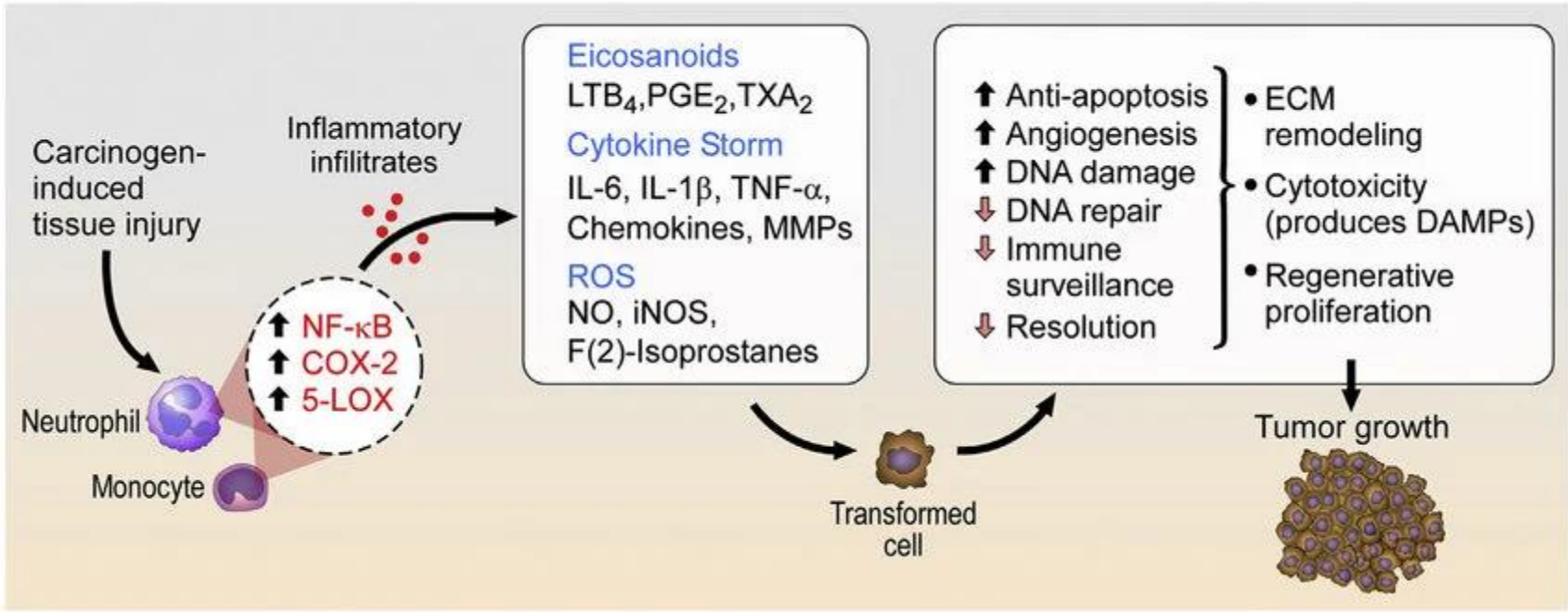
NON GENOTOXIC CARCINOGENICITY

- Every round of genome replication that precedes cell division is subject to the statistically unavoidable introduction of mutations



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NON GENOTOXIC CARCINOGENICITY



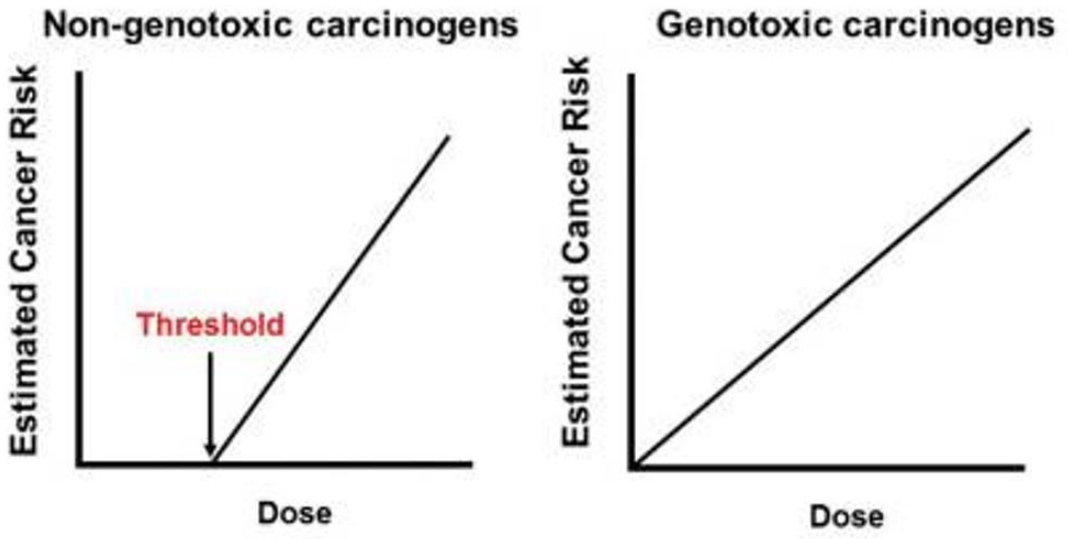
Fishbein, Anna & Hammock, Bruce & Serhan, Charles & Panigrahy, Dipak. (2020). Carcinogenesis: Failure of resolution of inflammation?. Pharmacology & therapeutics. 218. 107670. 10.1016/j.pharmthera.2020.107670.

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GENOTOXIC VS NON GENOTOXIC CARCINOGENS

- Genotoxic carcinogens typically induce tumours in multiple organs of rodents, may be carcinogenic to more than one species and to both males and females.
  - there is often evidence of a dose-response relationship for tumour induction, of the type that **does not suggest evidence of a threshold.**

- Non-genotoxic carcinogens are more likely to be characterised by tumour induction in a single species and/or in a single tissue and, commonly, in one sex only, often at low incidence and only at high dose with associated evidence of toxicity.
  - For non-genotoxic carcinogens **it may be possible to define a threshold**, i.e. a level of exposure below which the agent does not present a carcinogenic risk to humans



GENOTOXICITY TESTING AND CARCINOGENICITY

A major purpose of conducting *in vitro* genotoxicity assays is to be able to predict whether or not a chemical is a carcinogen without conducting a costly and time-consuming animal bioassay.

Children working as chimney sweeps often died from cancers

Percival Potts, 1775, linked occupational exposure to a specific cancer	Subsequently discovered that a chemical in soot, benzo[a]pyrene, causes animal cancers, as well as mutations in bacteria.	The concept of chemical carcinogenicity and the study of genetic toxicology were born

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GENOTOXICITY TESTING AND CARCINOGENICITY



Not all animal carcinogens are bacterial mutagens



Differences between animals and bacteria, including metabolism in the liver and other organs?



mammalian cell lines were developed, and liver extracts were included in test protocols



This combination of bacterial and mammalian cell tests produces the ‘desired’ positive results for about nine out of 10 carcinogens



This is not, however, as good a result as it seems, as this same combination also produces positive results for as many as nine out of 10 non-carcinogens



Finally, it was recognized that many carcinogens do not actually have a genotoxic mode of action

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LIMITATIONS

- “Where a compound known to be carcinogenic is not detected as a mutagen or genotoxin in such assays, or where a mutagen (or genotoxin) has been found to be non-carcinogenic, some sort of explanation needs to be sought”

Phillips, D. H., & Arlt, V. M. (2009). Genotoxicity: damage to DNA and its consequences.
In A. Luch (Ed.), Molecular, Clinical and Environmental Toxicology (Vol. 1, pp. 87-110). Birkhäuser Verlag.

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