The Chemistry of Cancer: What Causes It & How It Happens

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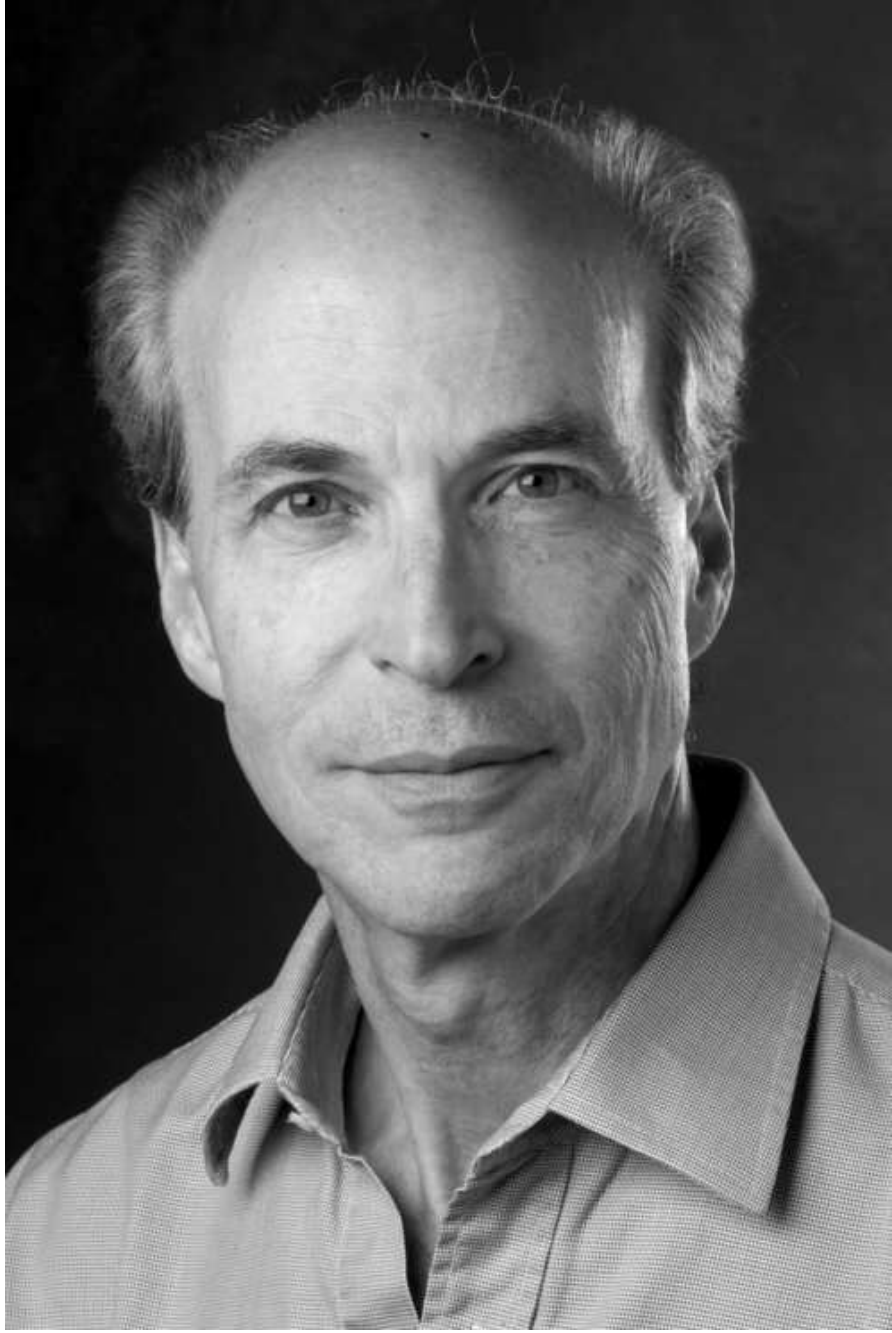
"…chemistry is really the queen of the sciences, chemistry is the common ground for all scientific investigation"

Roger D. Kornberg

Winner Nobel Prize in Chemistry 2006



Outlines

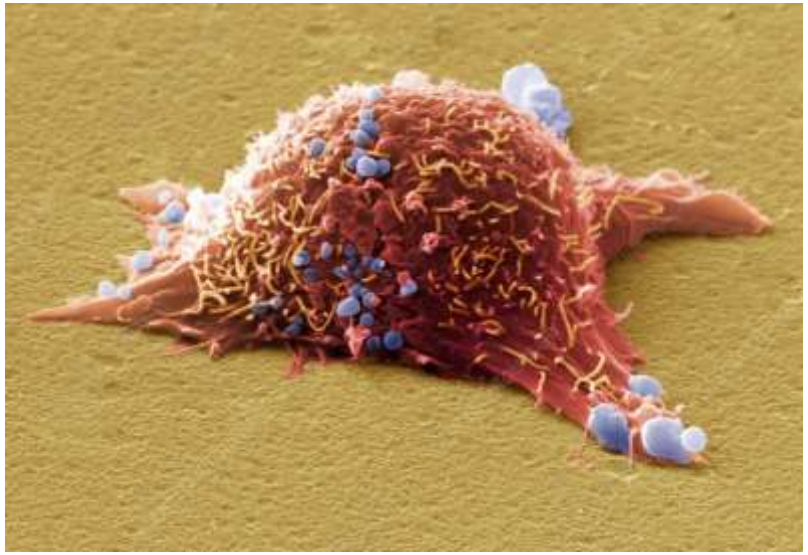
- Introduction
- Risk factors
- Chemical carcinogenicity
- Therapeutic application

Outcomes

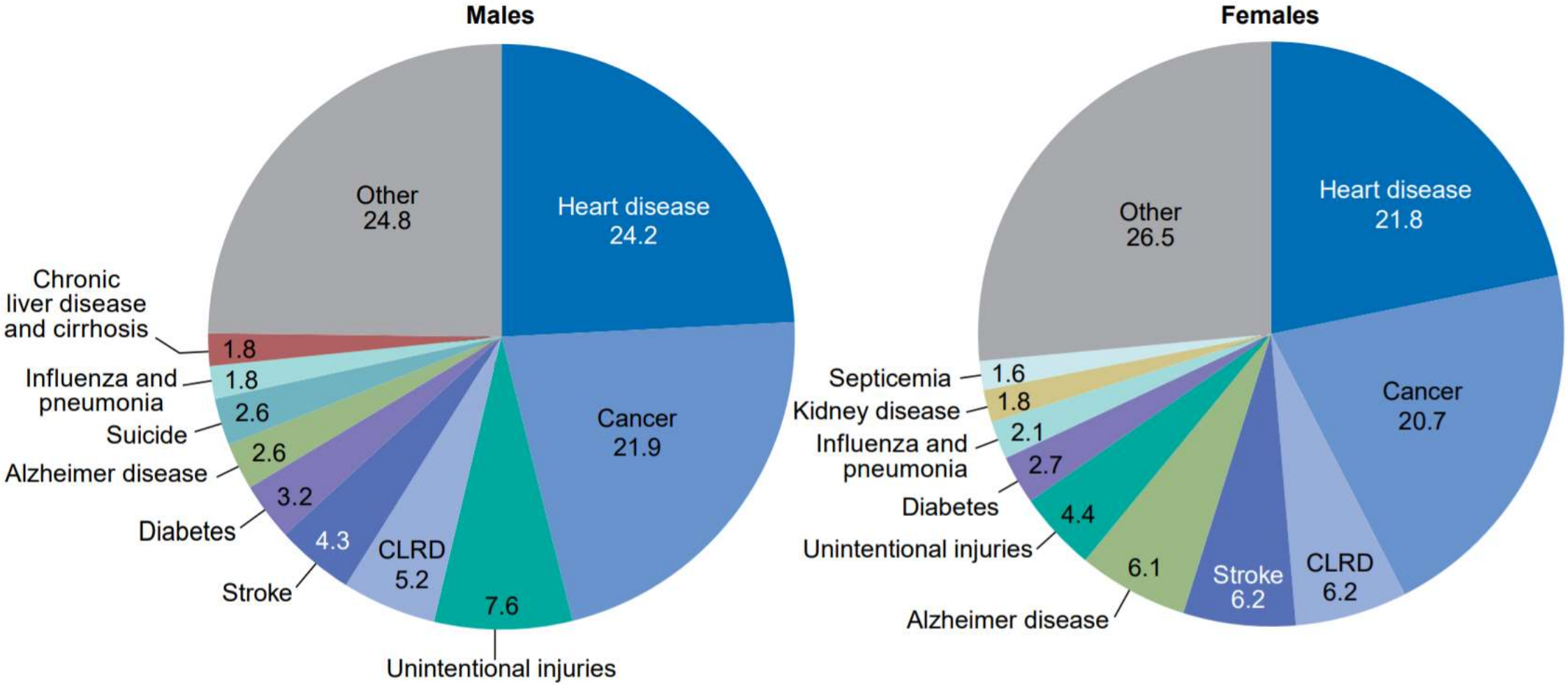
- Define carcinogenicity, electrophilicity, nucleophilicity
- Predict chemicals with carcinogenic properties
- Distinguish between different classes of carcinogens
- Describe mechanism of chemical carcinogenicity

What is cancer?

- WHO “a generic term for a large group of diseases that can affect any part of the body”
- NCI “a term for diseases in which abnormal cells divide without control and can invade nearby tissues. Cancer cells can also spread to other parts of the body through the blood and lymph systems”.

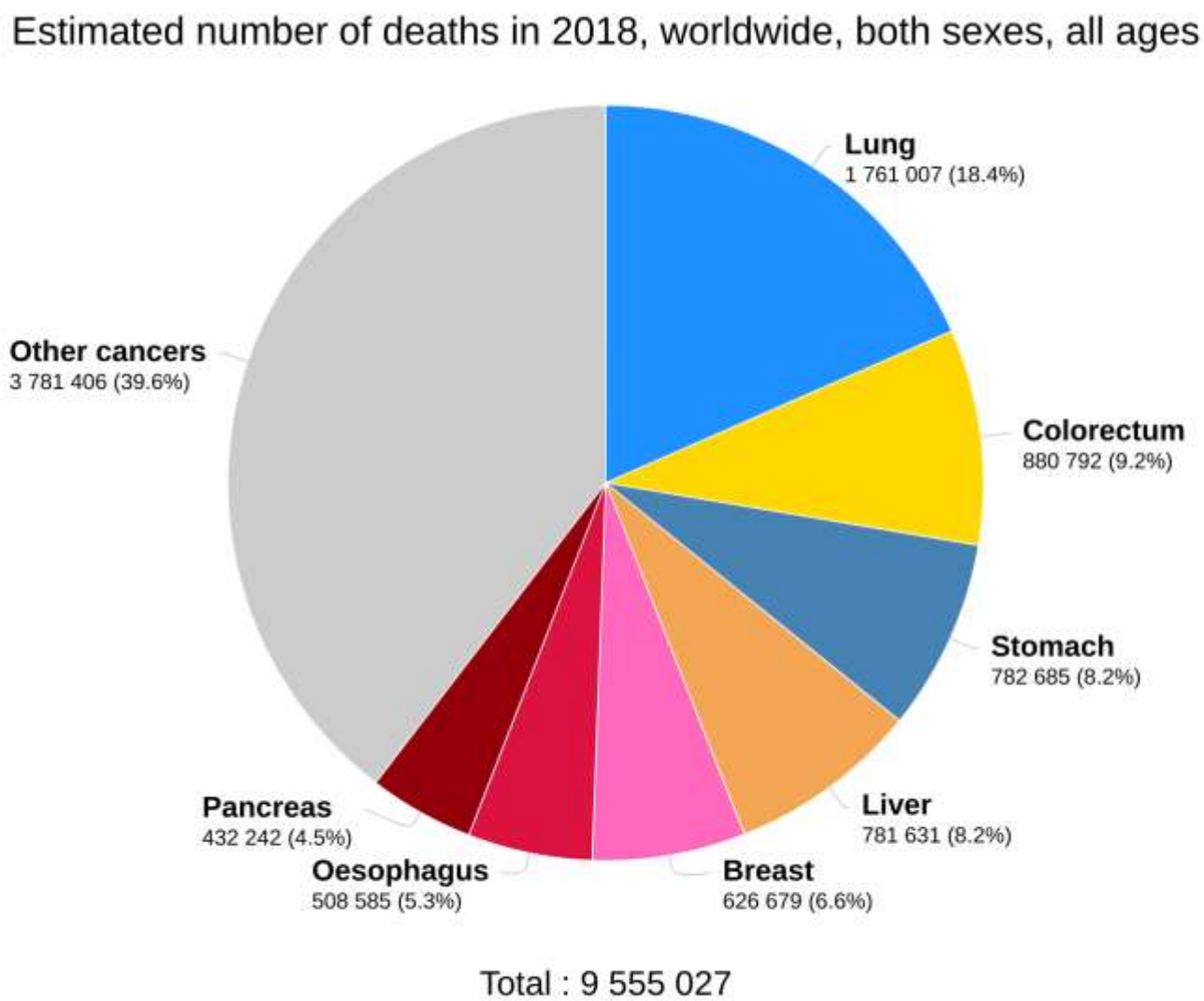


Key facts



NOTES: CLRD is Chronic lower respiratory diseases. Values show percentage of total deaths. Totals may not add to 100 due to rounding.
SOURCE: NCHS, National Vital Statistics System, Mortality.

Key facts



Data source: Globocan 2018
Graph production: Global Cancer Observatory (http://gco.iarc.fr)

International Agency for Research on Cancer
World Health Organization

Risk factors

Carcinogen

Carcinogen

- According to IUPAC in Glossary of Terms Used In Toxicology:

“Agent (chemical, physical, or biological) that is capable of increasing the incidence of malignant neoplasms, thus causing cancer”.

How to identify carcinogen?

- **I**nternational **A**gency for **R**esearch on **C**ancer (IARC):
  - Part of the WHO
  - Headquarter: Lyon, France
  - Founded in May 1965
  - Founding members: Germany, France, Italy, UK, USA

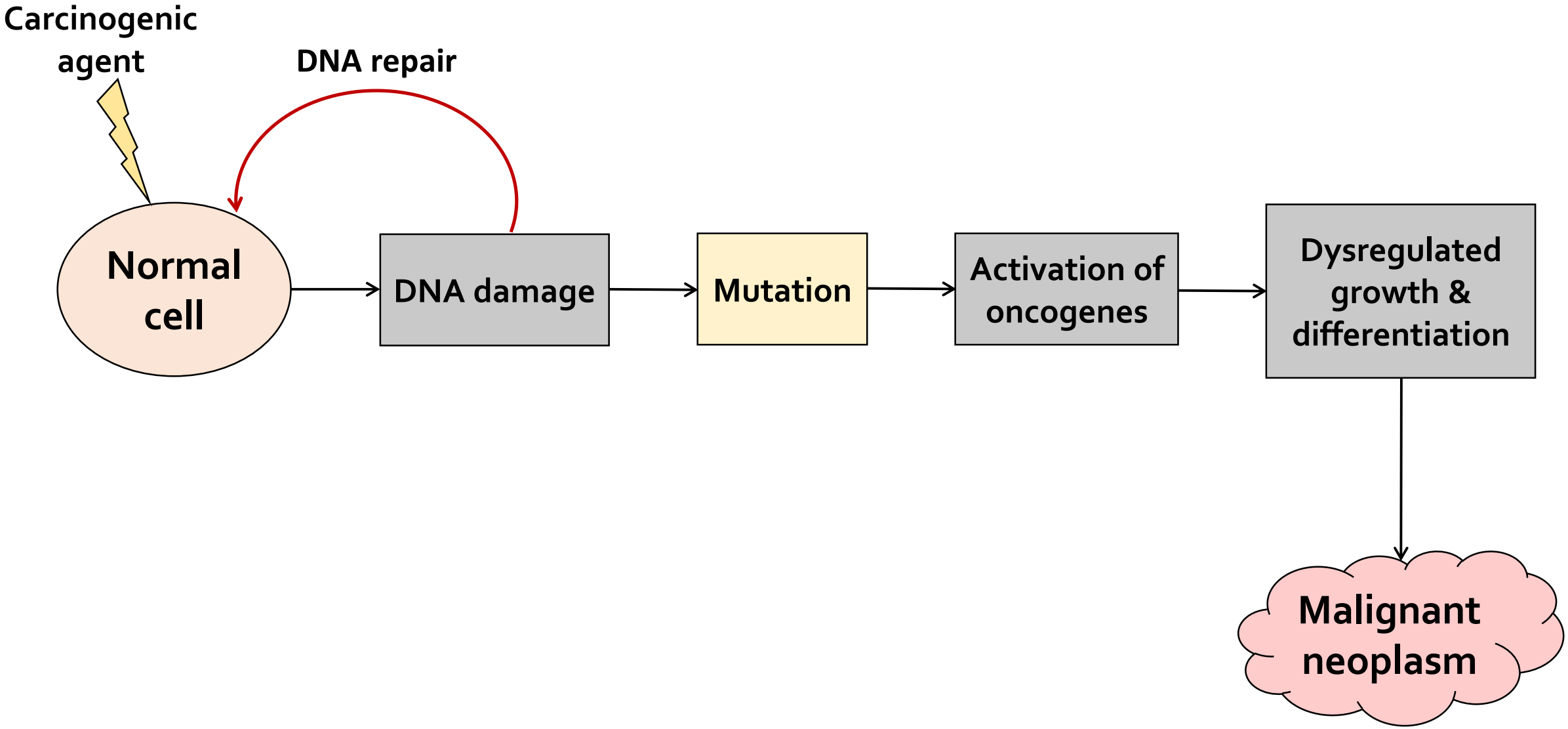
International Agency Research on Cancer

World Health Organization

IARC classification of carcinogens

Category	Definition	Agents	Example
Group 1	Carcinogenic to humans	121	Ethanol
Group 2A	Probably carcinogenic to humans	88	Acrylamide
Group 2B	Possibly carcinogenic to humans	313	Chloroform
Group 3	Not classifiable as to its carcinogenicity to humans	499	Coumarin

Carcinogenesis



Before “what makes a chemical carcinogen”

We have to know the chemistry of DNA

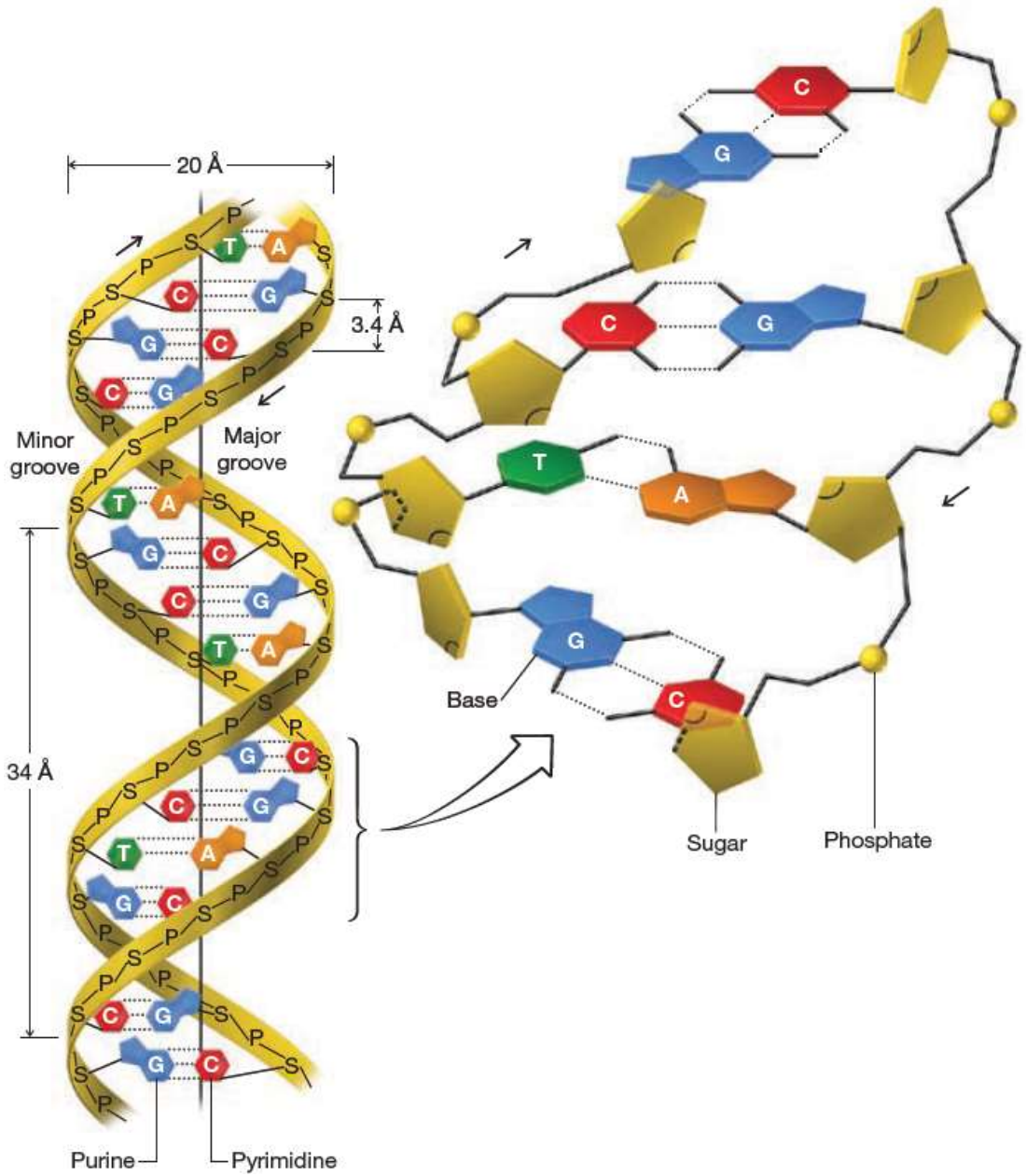
Cancer & Chemistry

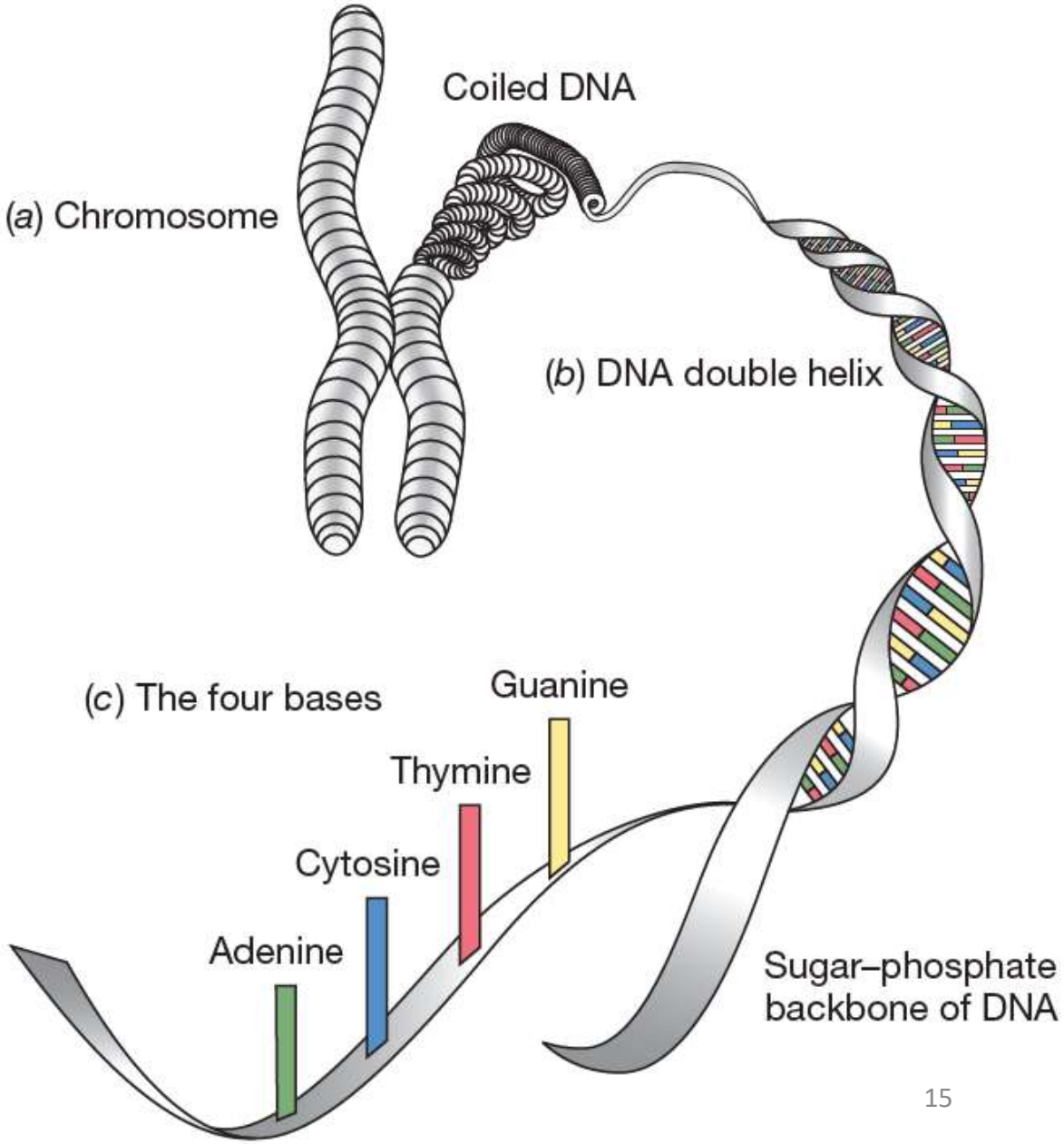
- To understand how cancer happens and how to treat it, you need to understand chemistry.
- In fact ..

Carcinogen + DNA → cancer

- *“There is a long-established and clear link between a chemical’s ability to bind covalently to DNA and genotoxicity”*

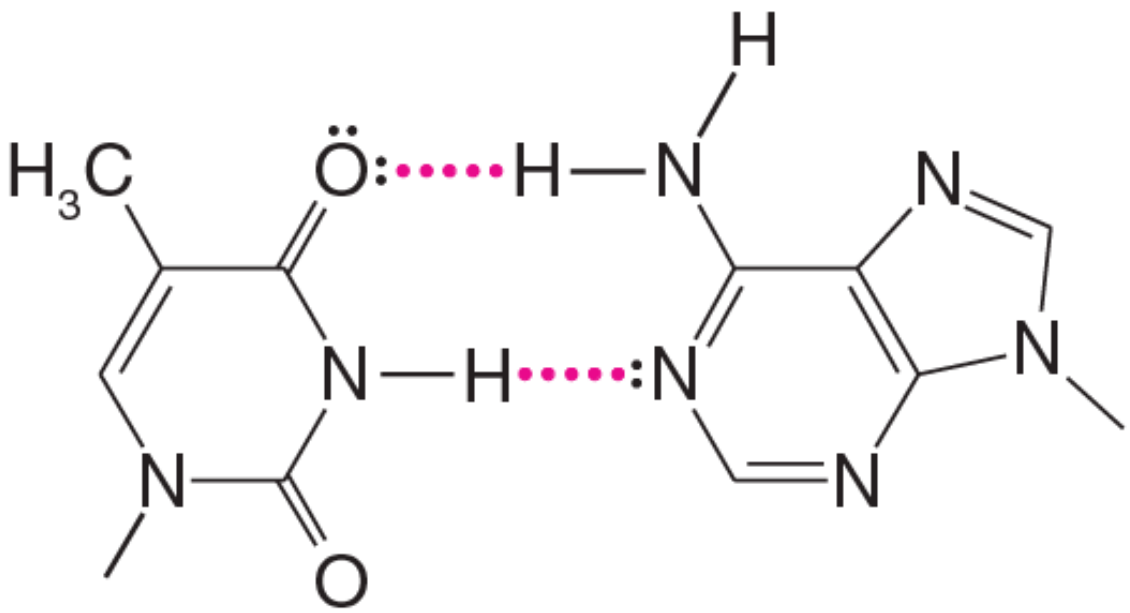
Nature of DNA





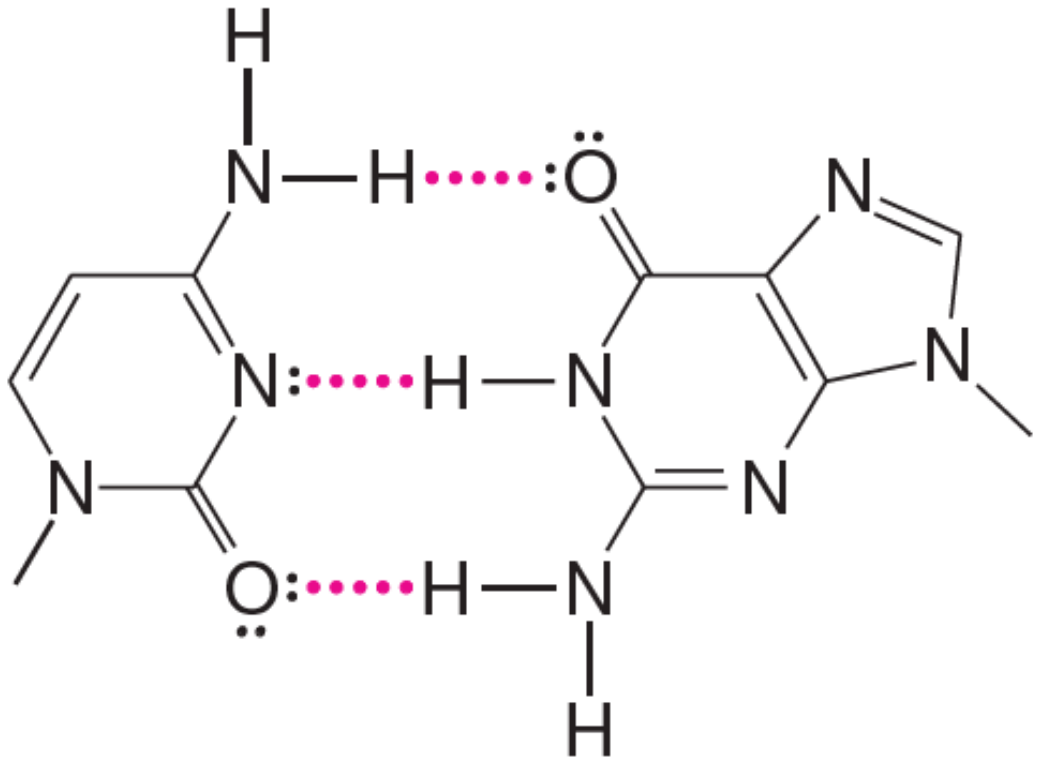
Nature of DNA

Adenine Pairs with Thymine



Thymine **Adenine**

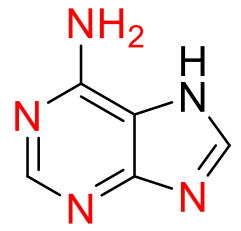
Guanine Pairs with Cytosine



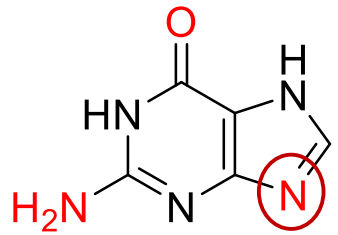
Cytosine **Guanine**

Nature of DNA

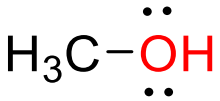
- DNA is considered as a **nucleophile** .. *"is a reagent that forms a bond to its reaction partner (the electrophile) by donating both bonding electrons".*

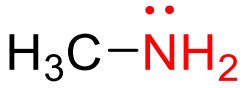


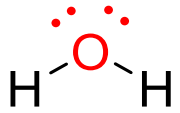
Adenine

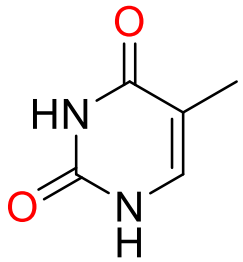


Guanine

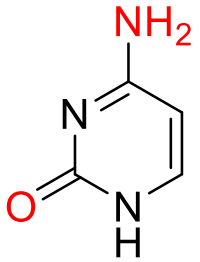








Thymine



Cytosine

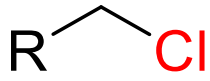
What makes a chemical carcinogen?

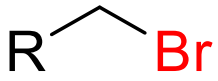
Elizabeth C. Miller (1920–1987) & James A. Miller (1915–2000)

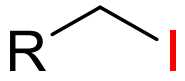
What makes a chemical carcinogen?

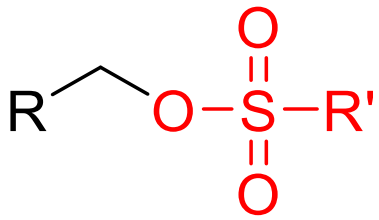
- A molecule would be considered as a carcinogen if it is **electrophile** or **metabolized into reactive electrophilic metabolite**.
- Electrophile is "*a reagent that forms a bond to its reaction partner (the nucleophile) by accepting both bonding electrons from that reaction partner".*

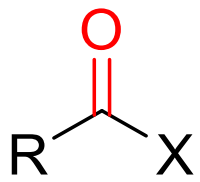
What makes a chemical carcinogen?

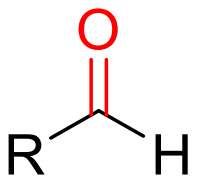


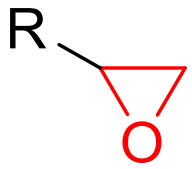


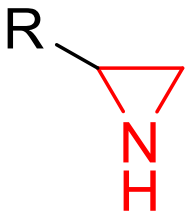


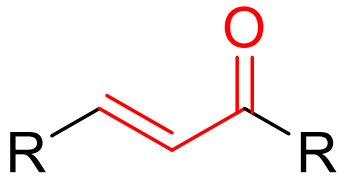






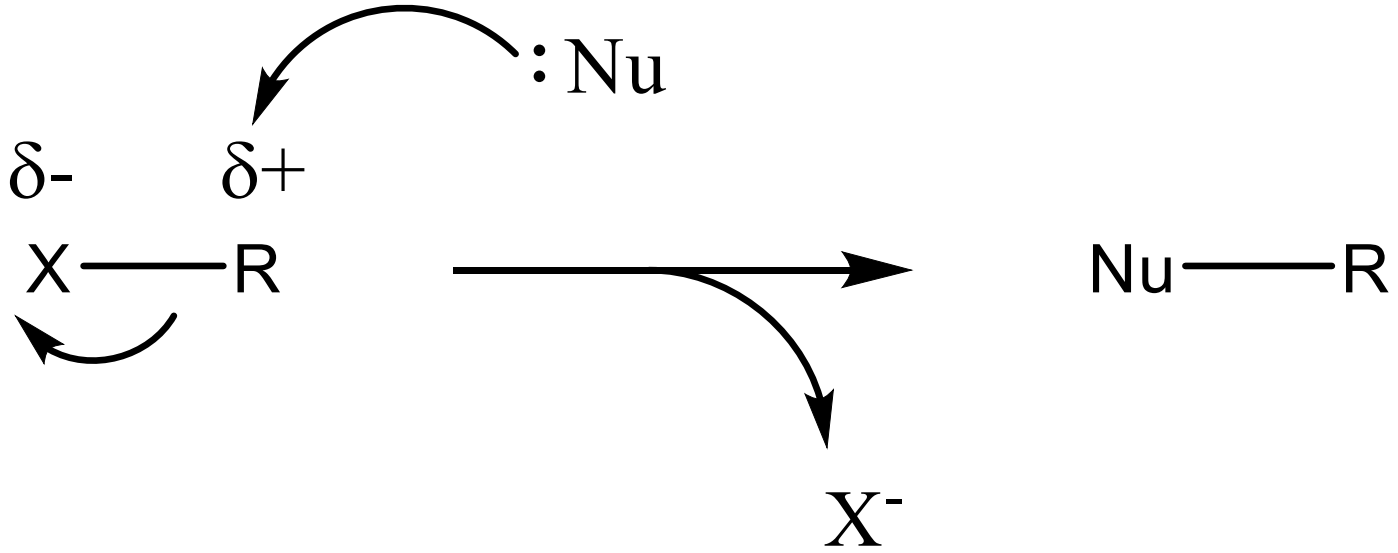




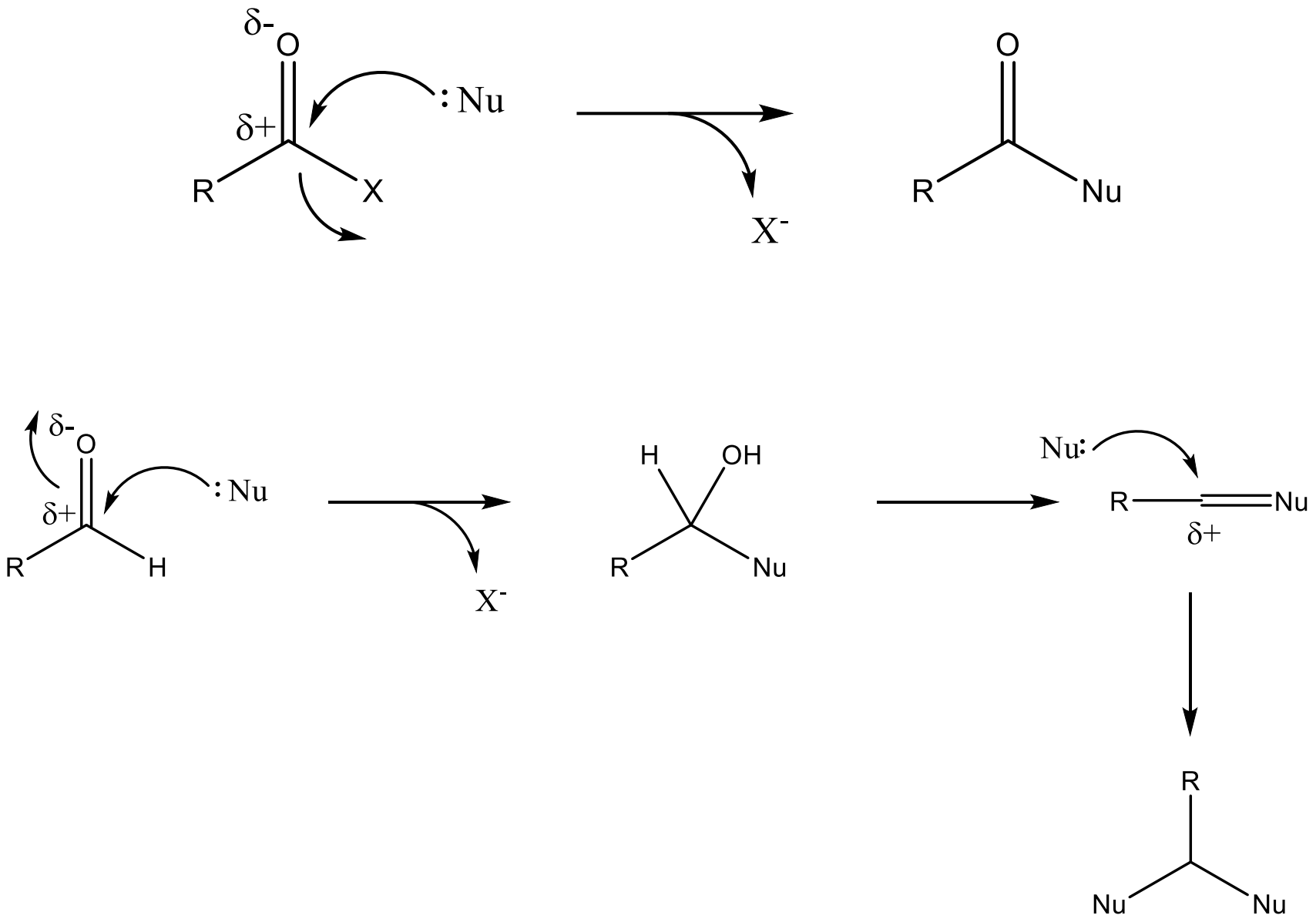


Mechanism of carcinogenesis: Alkyl halides & sulfonates

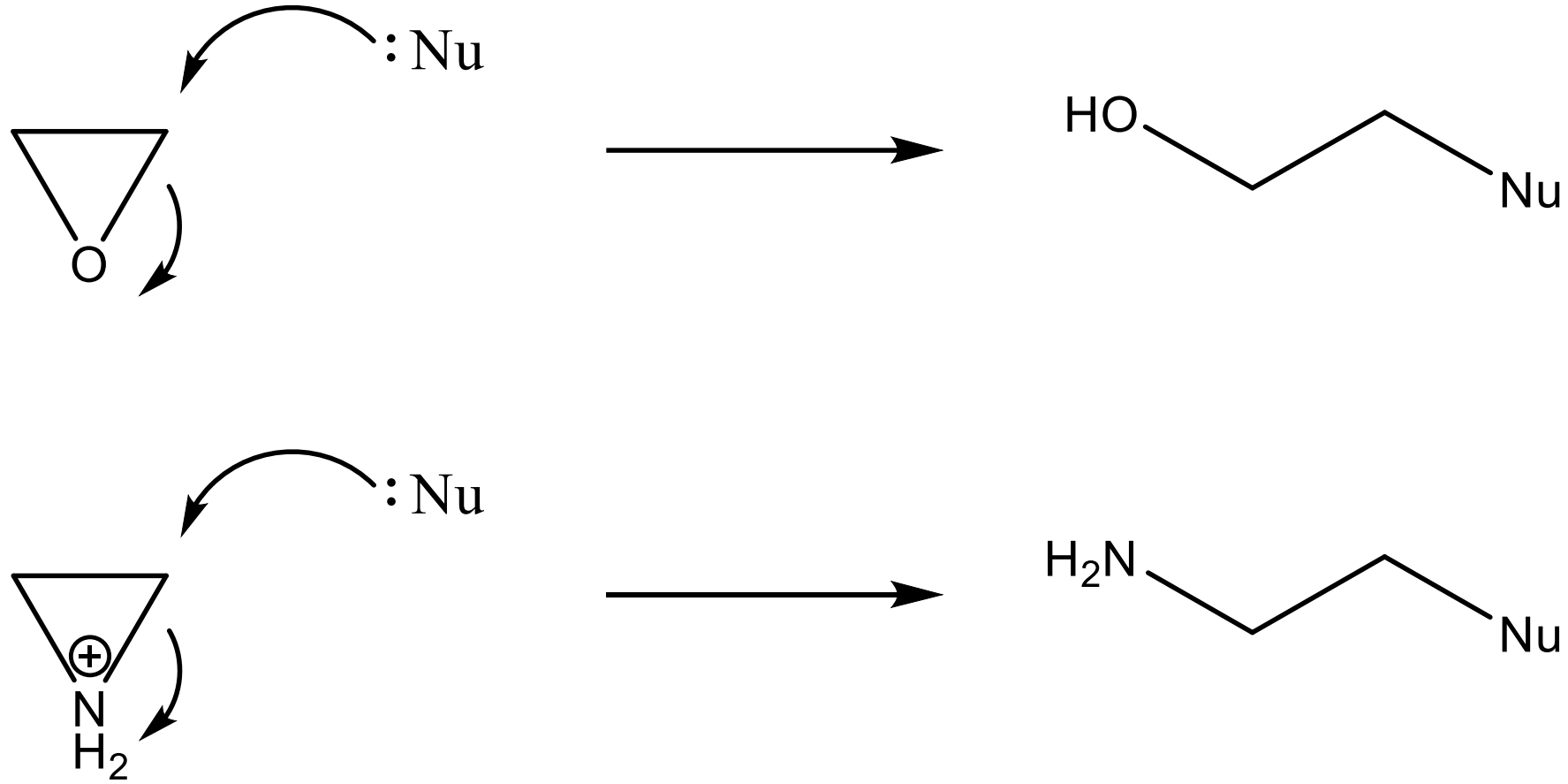
- It is simply nucleophilic substitution reaction.
- They mainly but not exclusively alkylate N^7 of G.



Mechanism of carcinogenesis: Carbonyl compounds

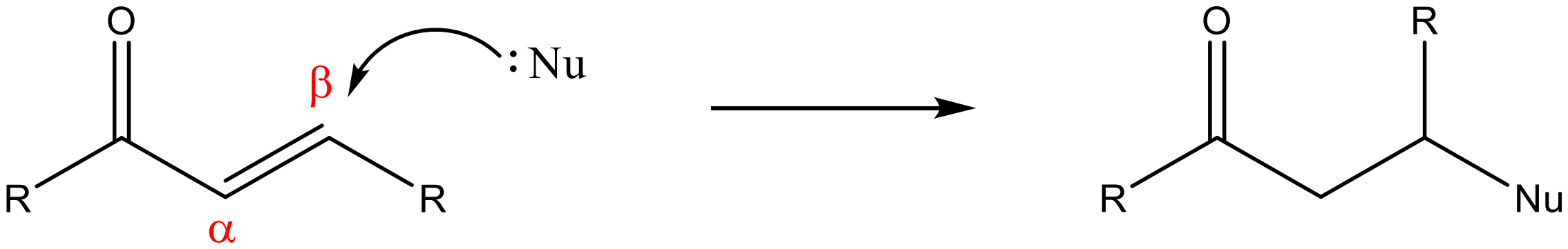


Mechanism of carcinogenesis: Aziridines & epoxides



Mechanism of carcinogenesis: Michael acceptors

- The toxicity occurs due to conjugate addition.

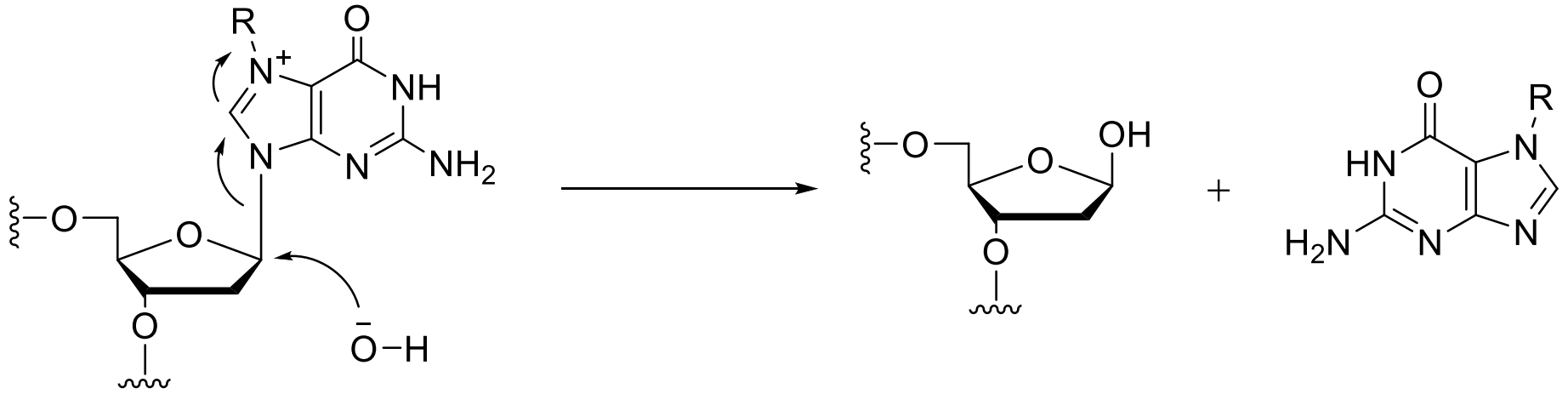


Consequences of DNA alkylation

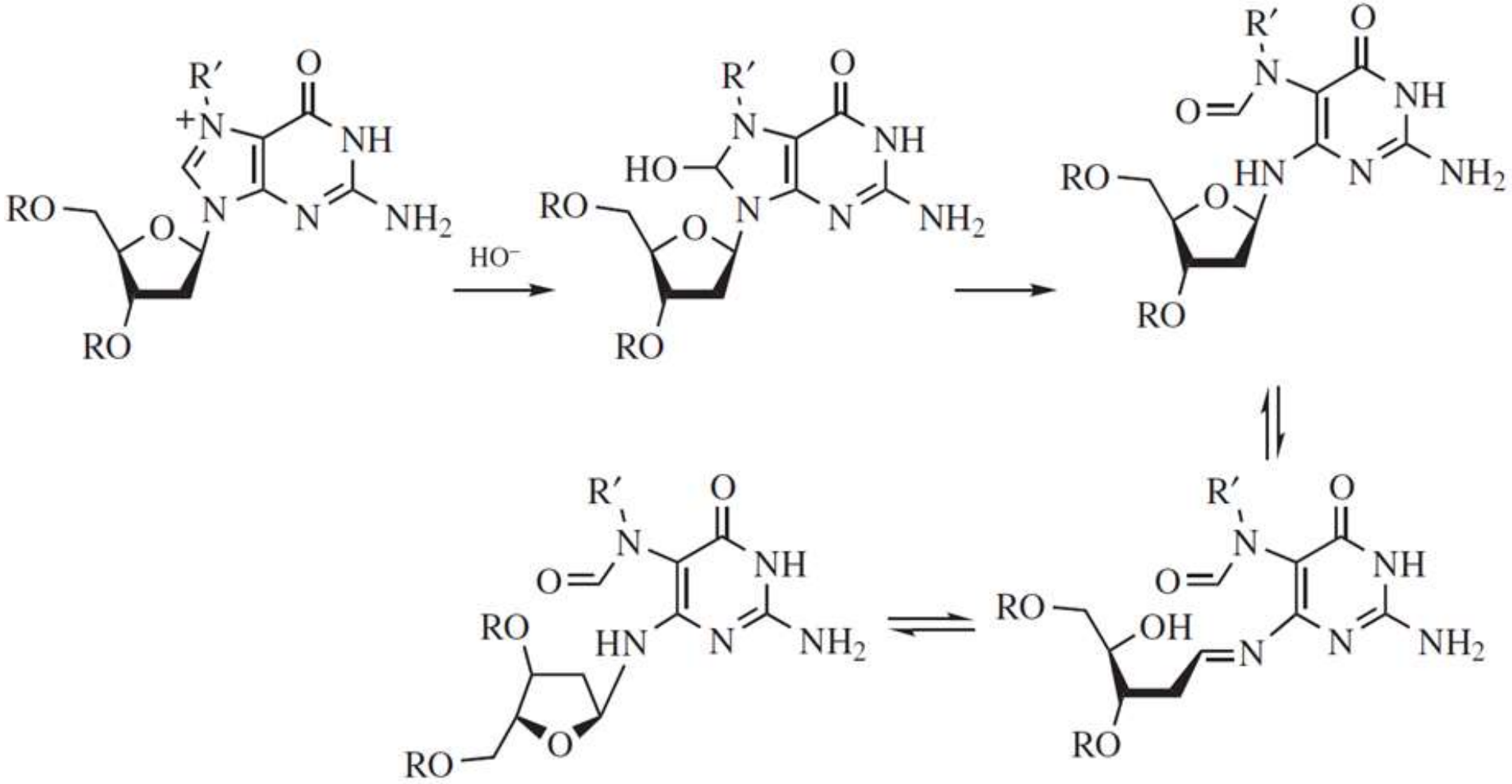
- Alkylation of DNA causes DNA damage in which *“attempts to replicate damaged DNA, polymerases may introduce errors into the genetic code (mutagenesis)”*.

Consequences of DNA alkylation

- Alkylation converts the base to an effective leaving group so that attack by water leads to depurination.



Consequences of DNA alkylation: Ring opening



Mechanism of carcinogenesis

- Chemical carcinogens can be:
  - ***Genotoxic****: Electrophilic species that interact with DNA covalently (most common & well studied).*
  - ***Nongenotoxic****: Act by a variety of mechanisms with no apparent unifying concept.*

Mechanism of carcinogenesis

CHEMICAL REVIEWS

REVIEW

pubs.acs.org/CR

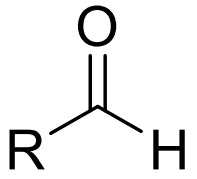
Mechanisms of Chemical Carcinogenicity and Mutagenicity: A Review with Implications for Predictive Toxicology

Romualdo Benigni* and Cecilia Bossa

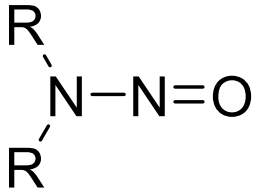
Istituto Superiore di Sanita', Environment and Health Department, Viale Regina Elena, 299 00161 Rome, Italy

Genotoxic carcinogens: Cigarettes

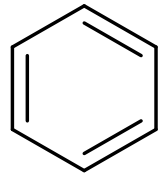
Ethylene oxide



Aldehydes

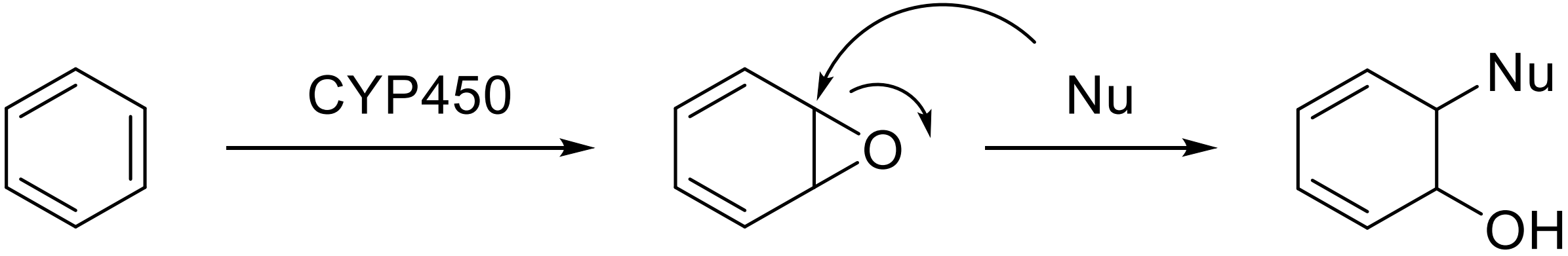


N-nitrosamines

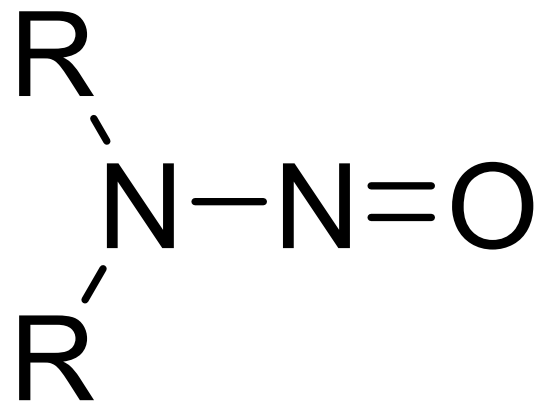


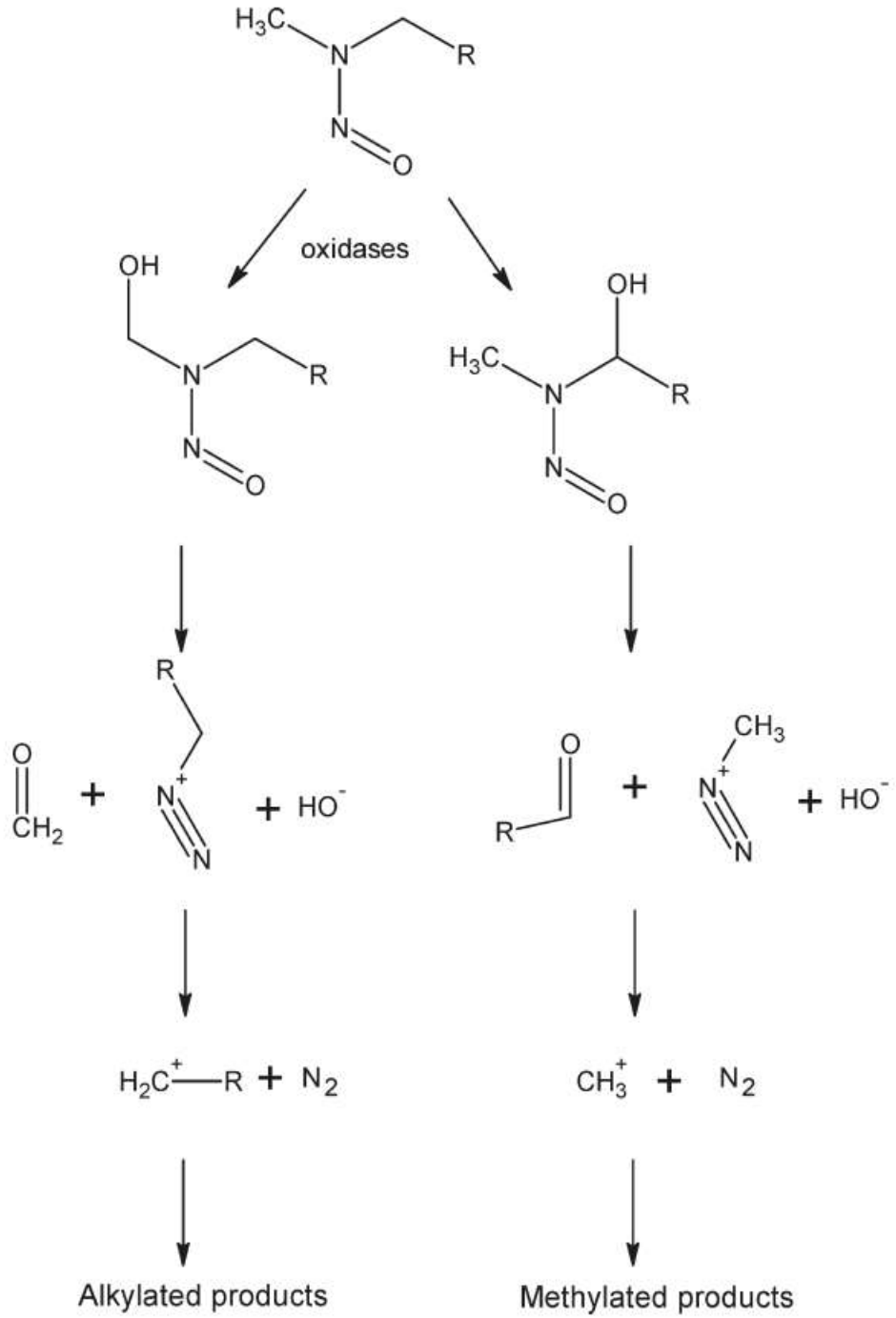
Benzene

Genotoxic carcinogens: Cigarettes



Genotoxic carcinogens: Cigarettes

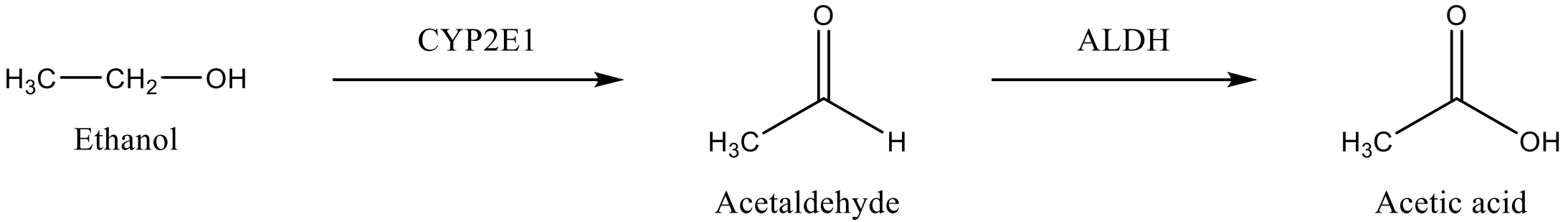




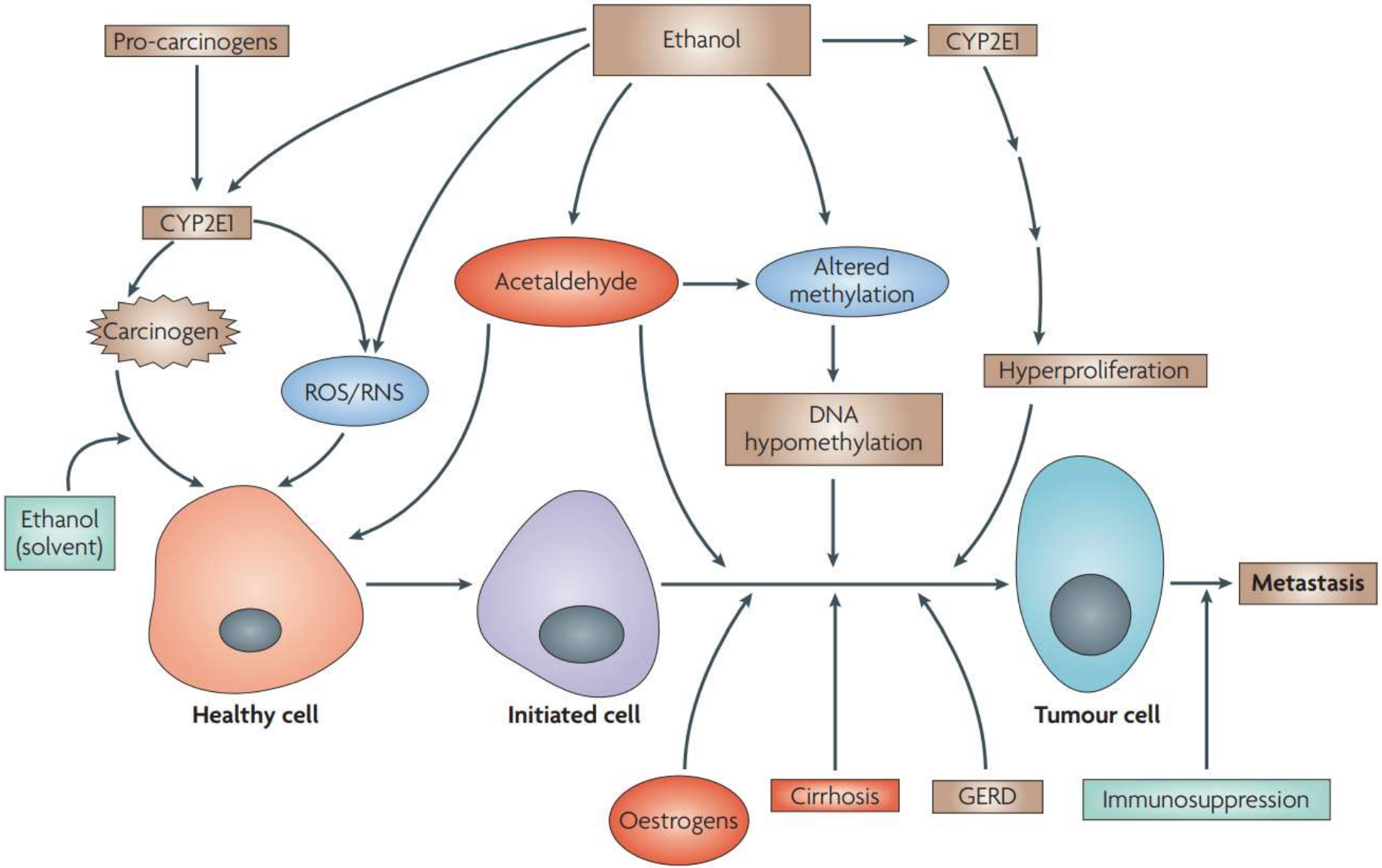
Genotoxic carcinogens: Alcohol

Ethanol

Genotoxic carcinogens: Alcohol



Genotoxic carcinogens: Alcohol

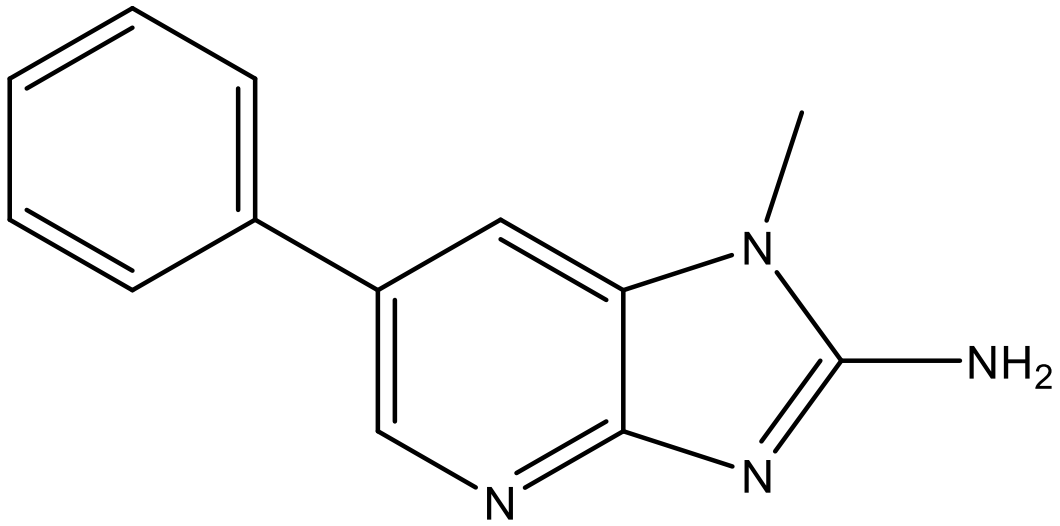


Genotoxic carcinogens: Diet

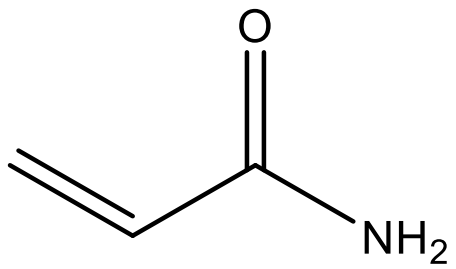
Genotoxic carcinogens: Diet

- Cooking at high temperature for long time produce significant amount of carcinogens:
  - Heterocyclic aromatic amines (HAA): PhIP
  - Acrylamide
  - *N*-nitroso compounds

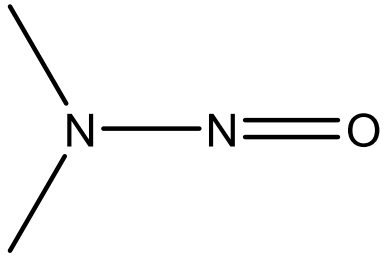
Genotoxic carcinogens: Diet



PhIP

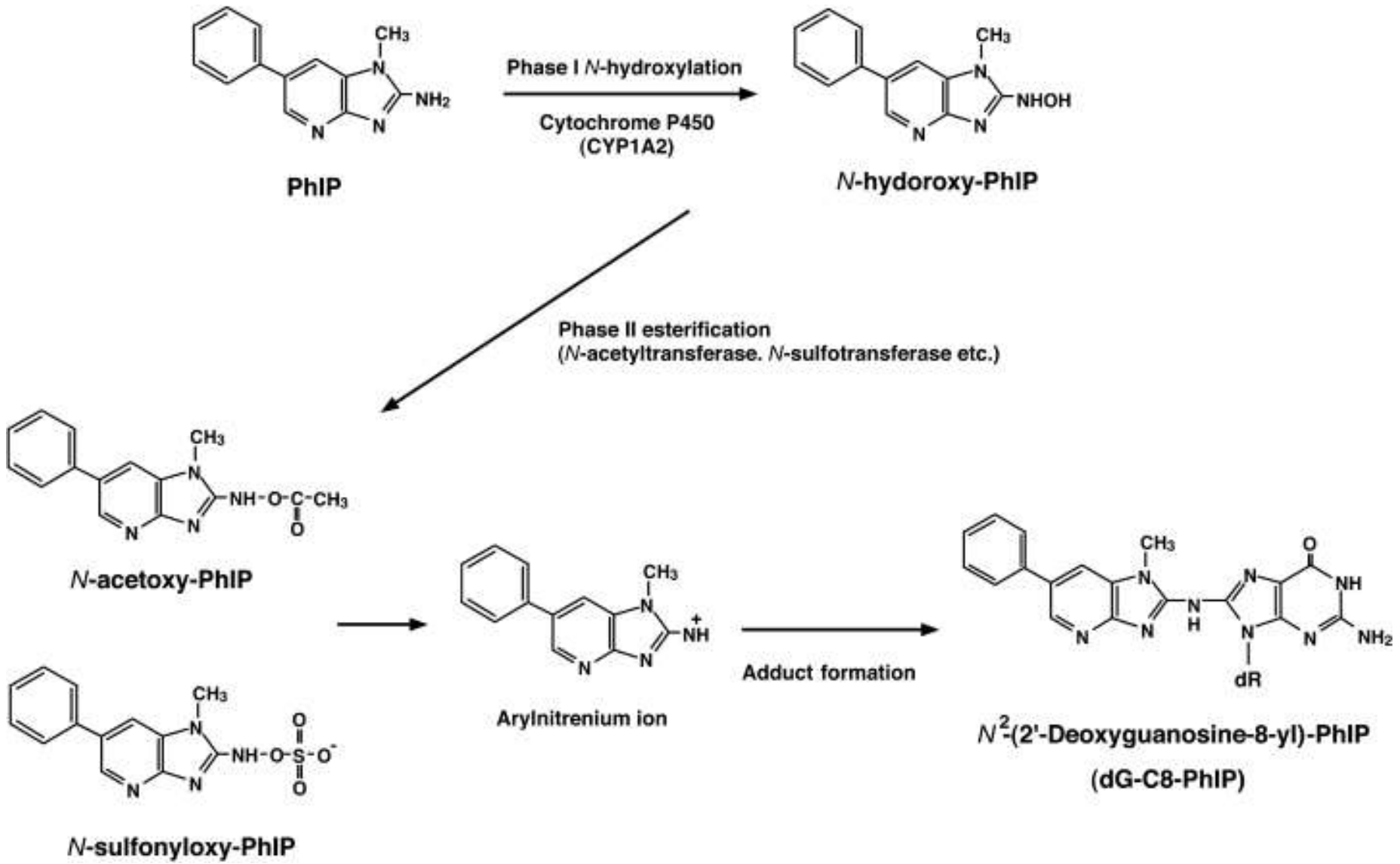


Acrylamide



NDMA

Genotoxic carcinogens: Diet

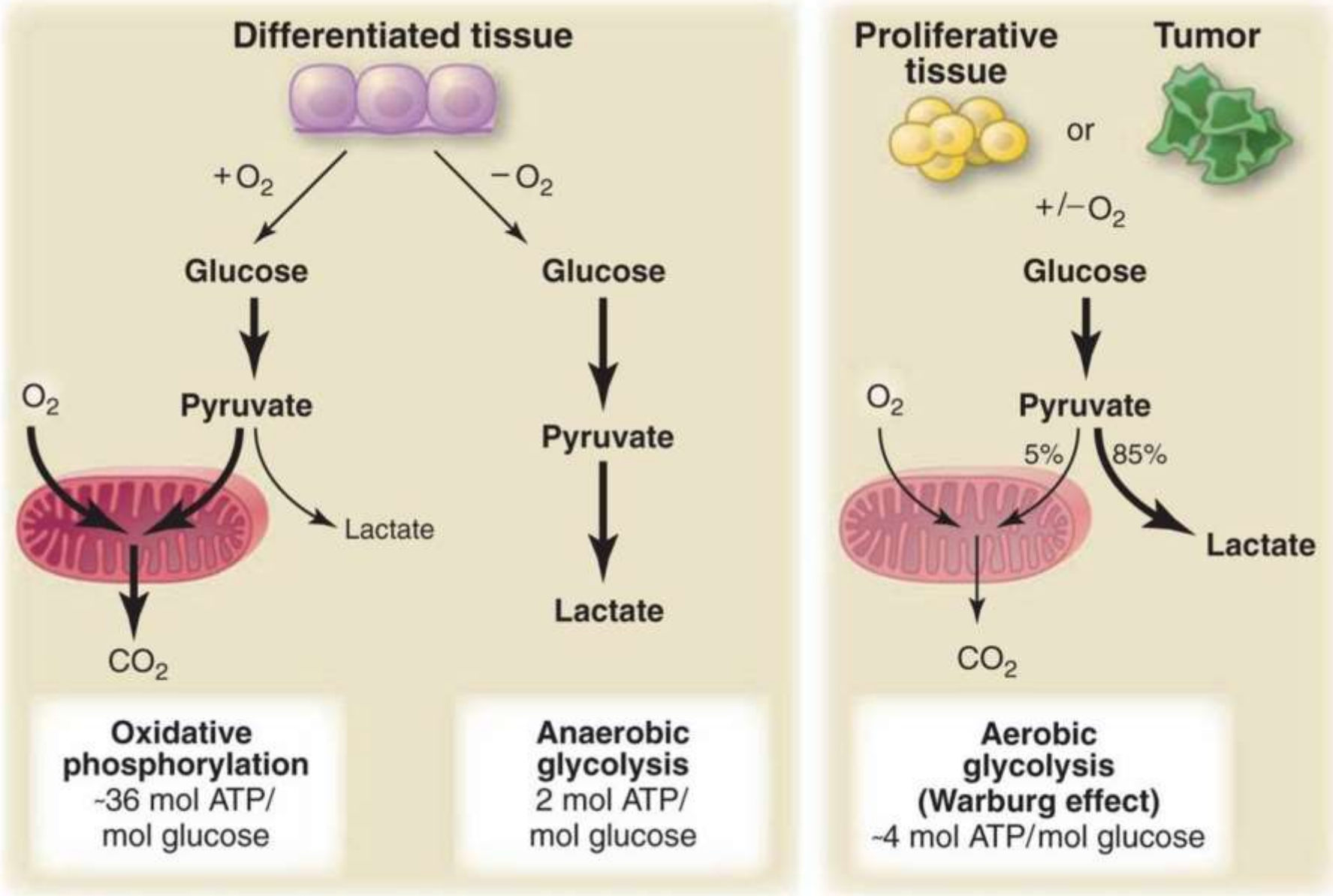


Chemistry of cancer microenvironment

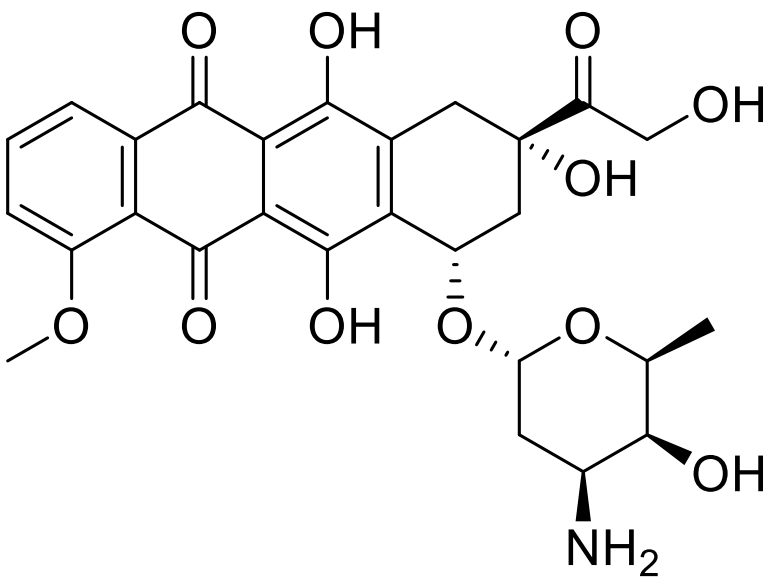
Changes in metabolism is one of the hallmarks of cancer

- Under aerobic conditions, normal cells metabolize glucose to pyruvate (aerobic glycolysis).
- Pyruvate is converted to lactate only under anaerobic conditions (anaerobic glycolysis).
- Cancer cells, however, metabolize glucose to lactate.
- This will decrease the pH of tumour microenvironment (slightly acidic).
- This is called **Warburg effect**.

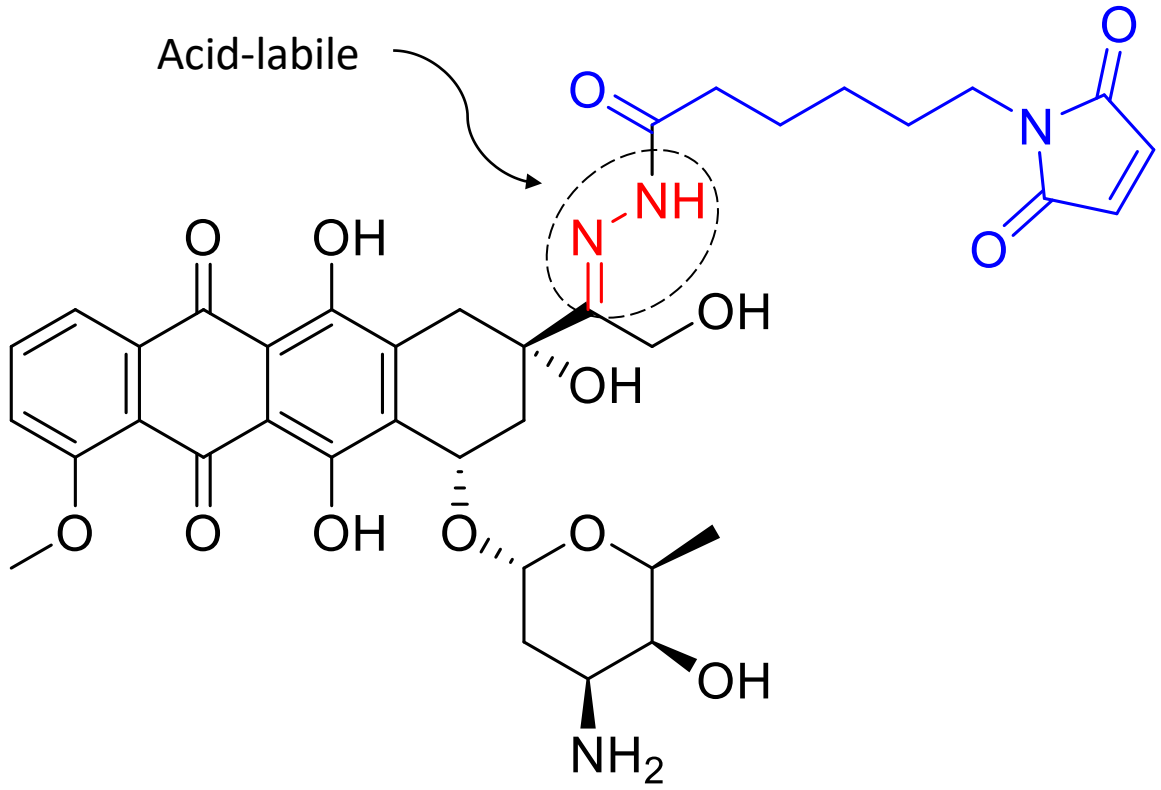
Warburg effect



Can these changes be exploited?

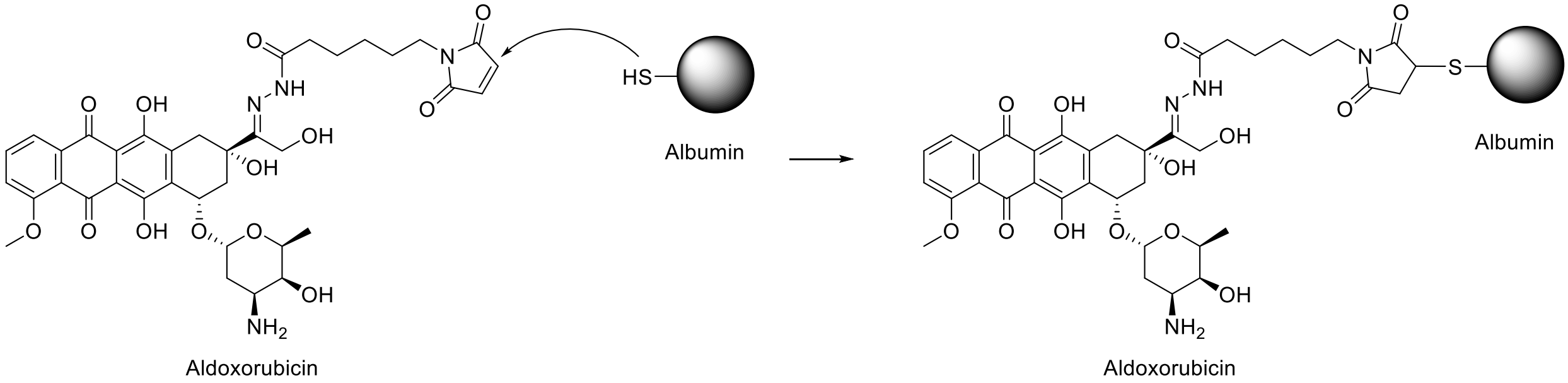


Doxorubicin
(Cardiotoxic)

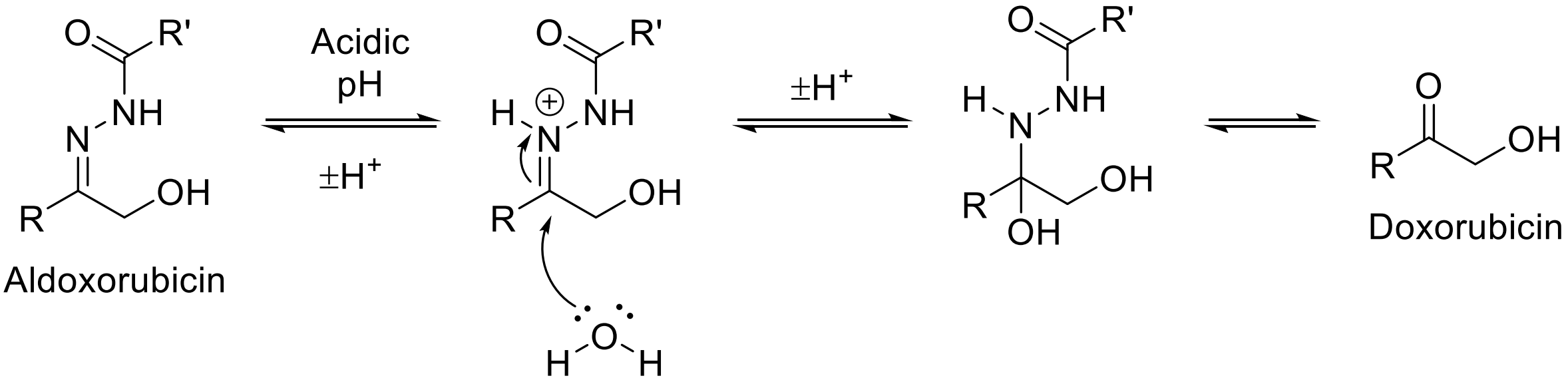


Aldoxorubicin

Aldoxorubicin has superior safety with respect to cardiotoxicity



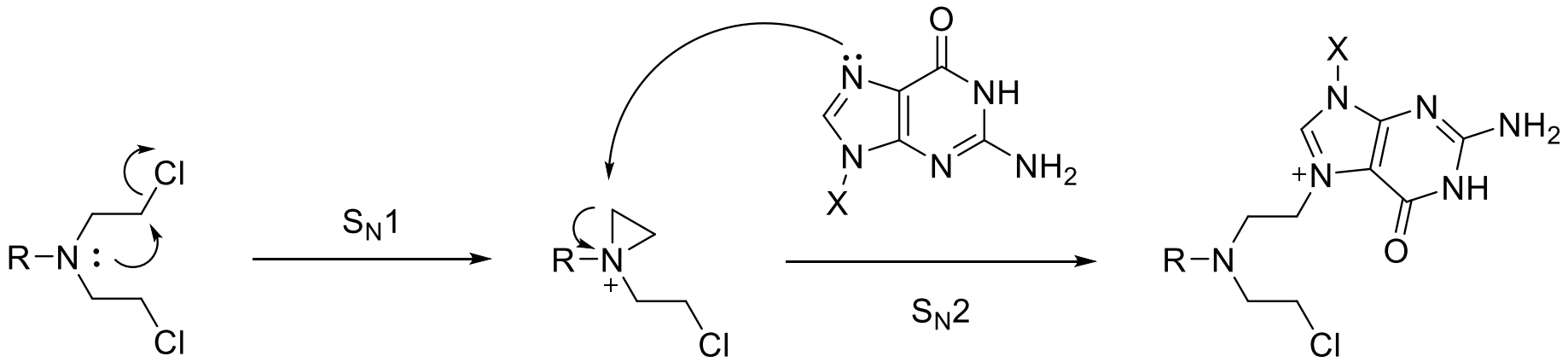
Aldoxorubicin has superior safety with respect to cardiotoxicity

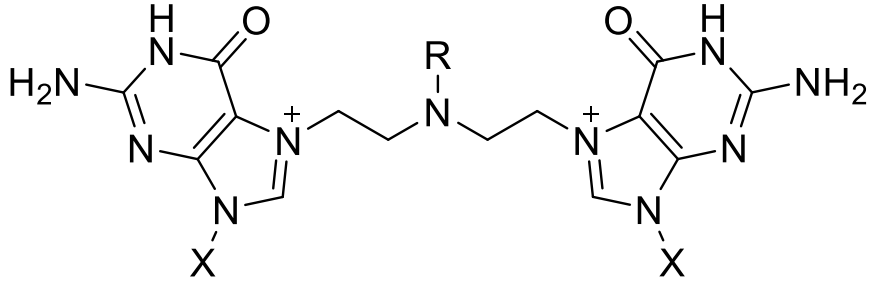


Reactive oxygen species (ROS) and cancer

- Unlike normal cells, cancer cells are characterized by increased levels of ROS, such as H_2O_2.
- This will lead to oxidative damage (oxidative stress).

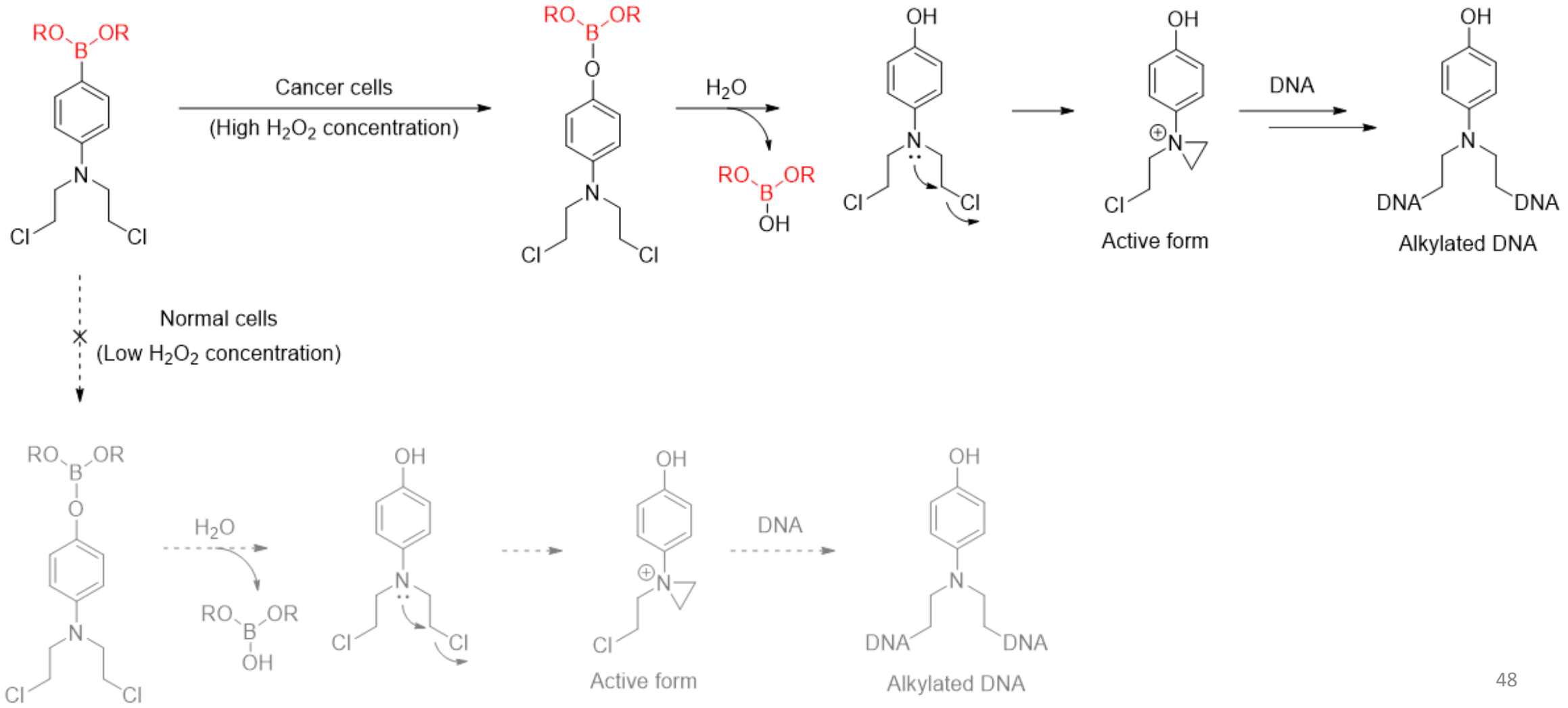
Can these changes be exploited?





cross-linked DNA

Cancer cell-specific alkylating agents



In conclusion

- Cancer is “a product of a chemical reaction between DNA & a carcinogen”.
- Most carcinogens are either electrophilic in nature or metabolized to reactive electrophilic metabolites.
- Understanding chemical changes in cancer cells has helped in designing drugs with lower side effects.

Thank you ☺