# Chemical Carcinogenicity Revisited 2: Current Knowledge of Carcinogenesis Shows that Categorization as a Carcinogen or Non-Carcinogen is Not Scientifically Credible

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RASS 11/13/19

# Classification of Carcinogens: What Could Go Wrong ?

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EUROTOX WORKSHOP 2019

# There certainly are anomalies

## How did we explain this?

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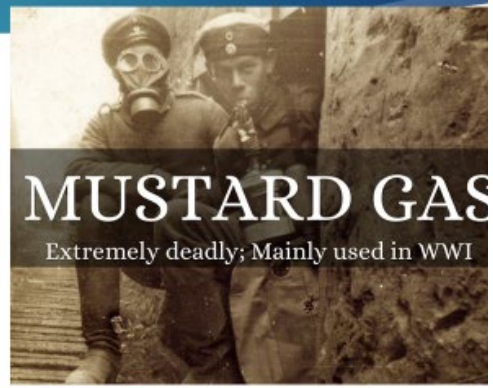


"UN health body says bacon, sausages and ham among most carcinogenic substances along with cigarettes, alcohol, asbestos and arsenic." Guardian



## All "Carcinogens" Are Not Equal

**IARC 2A**

- Several PAH
- Nitrosoamines (NDMA, MMS, DEN)
- Adriamycin
- Glyphosate
- Red meat
- Hairdresser or Barber

**IARC 2B**

- Kepone
- Ethylymethanesulphonate
- Riddelline
- Chloroform
- Gasoline
- Coffee

Incomplete information; may be misleading

# Classification for Carcinogenicity

## Evidence Maps to Cancer Classifications

| Human | Animal | Indirect, Other | IARC | US EPA | NTP |
|---|---|---|---|---|---|
| Sufficient | -- | -- | Carcinogenic to humans (Group 1) | Carcinogenic to humans | Known to Be Human Carcinogen |
| Limited | Sufficient | Strong human mechanistic data | | | |
| | | -- | Probably carcinogenic to humans (Group 2A) | Likely to be carcinogenic to humans | Reasonably Anticipated to Be Human Carcinogen |
| Inadequate | Sufficient | Strong | | | |
| | Limited | Strong | Possibly carcinogenic to humans (Group 2B) | | |
| | Sufficient | -- | | | |
| Limited | Limited | -- | | | |
| Inadequate | Inadequate | Strong & same class as other carcinogens | | | |
| | | Strong/ convincing | | Inadequate Information to Assess | |
| Inadequate | Limited | -- | Not classifiable | Suggestive | Not classified |

Zeise EEA Copenhagen Sept 3, 2010

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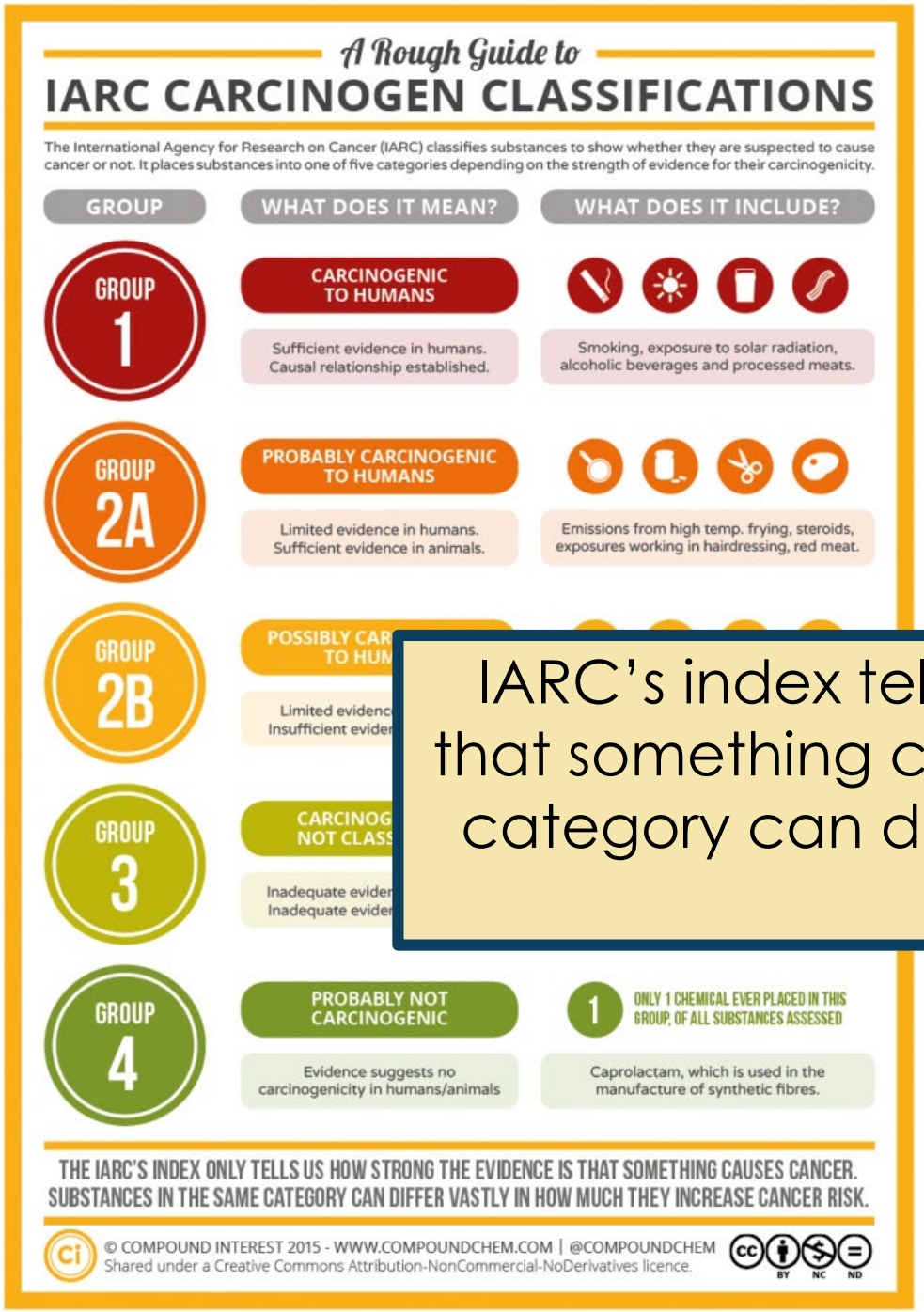
- Many schemes – IARC, GHS, EU but use same basic concept
- Grade the strength or weight of evidence not carcinogenic potential
- Potency difference of $10^8$ in chemicals in same category
- Chemicals are carcinogens or non-carcinogens




## Agents Classified by the IARC Monographs, Volumes 1–119

| | | |
|---|---|---|
| **Group 1** | **Carcinogenic to humans** | **120 agents** |
| Group 2A | Probably carcinogenic to humans | 81 |
| Group 2B | Possibly carcinogenic | 299 |
| | ty to humans | |
| Group 4 | Probably not carcinogenic to humans | **1** |

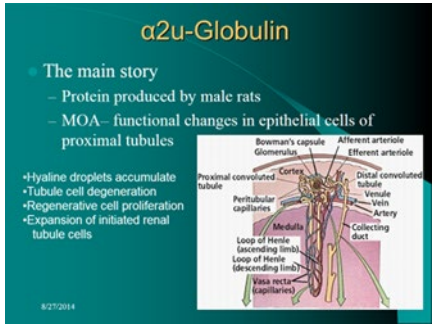
IARC's index tells us only how strong is the evidence that something causes cancer. Substances in the same category can differ vastly in how much they increase cancer risk.

http://www.compoundchem.com/2015/10/26/carcinogens/

# Evidence for Carcinogens

- Epidemiology – mainly evidence for carcinogenicity, not lack of carcinogenicity – difficult to prove negative
- Rodent bioassays
  - Treatment related increase in neoplasms – CARCINOGEN*
  - No treatment related increase in neoplasms – NON-CARCINOGEN

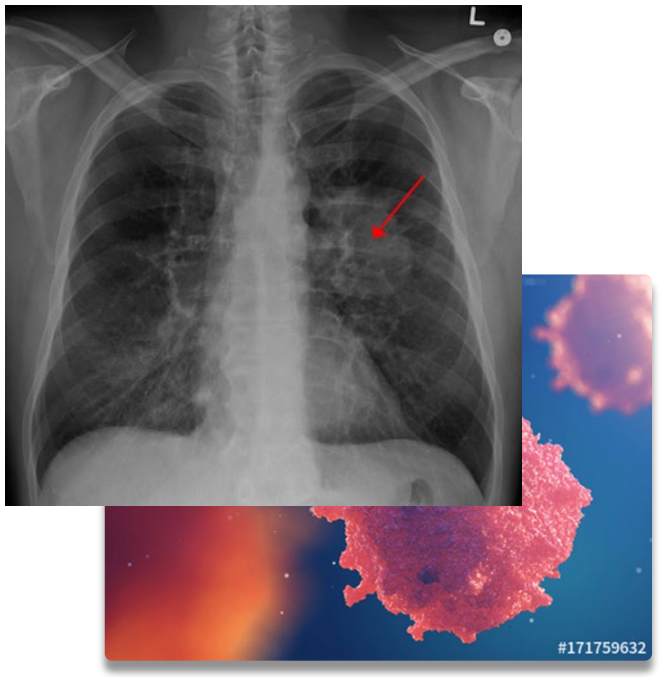
*Unless human non-relevance can be proved



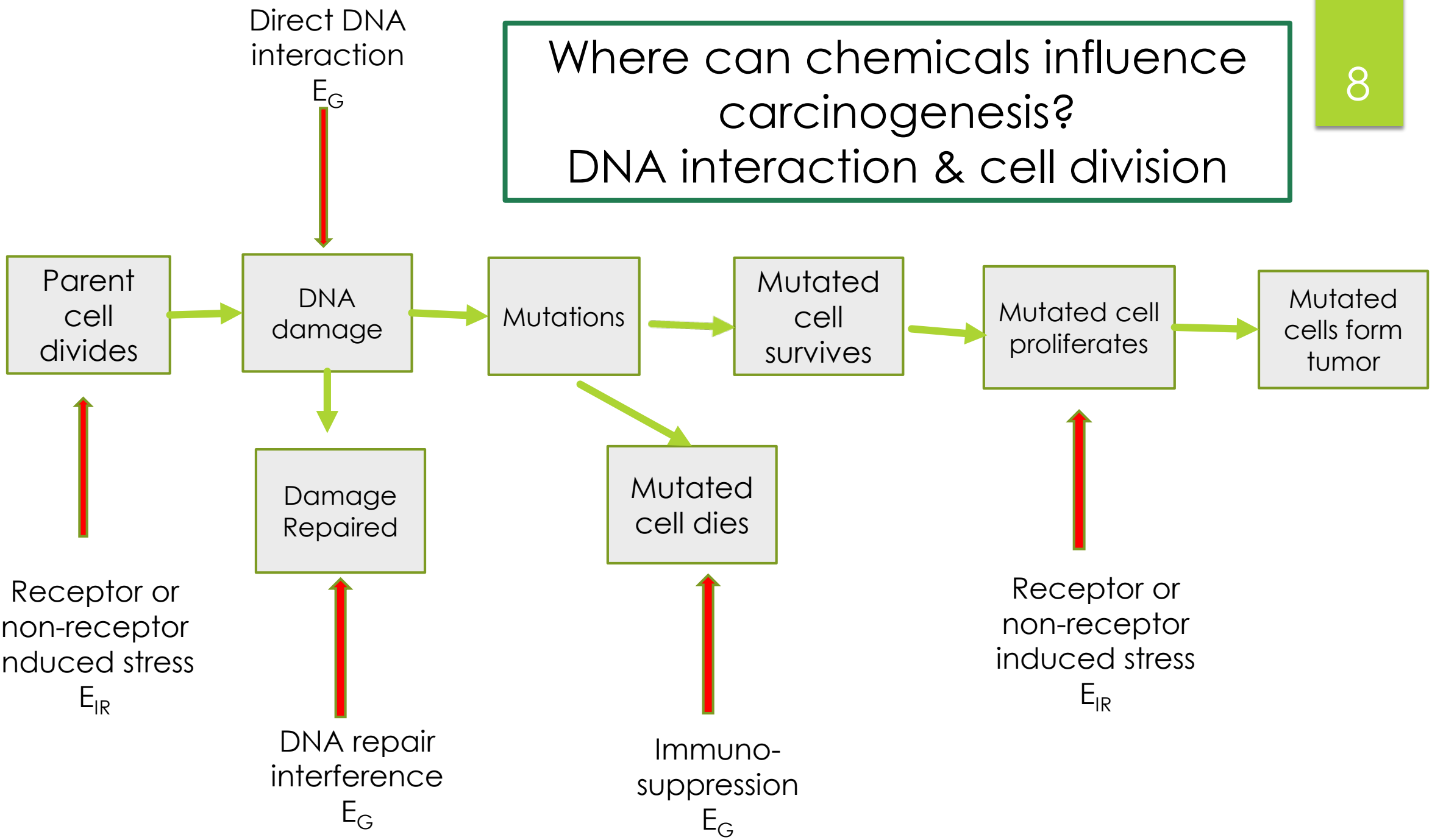

What about decreases in neoplasms?

# What is known about the cancer process?

- Cancer is due to mistakes occurring in the DNA.
- More than one mistake in the DNA is necessary.
- All of the mistakes need to accumulate in a single cell (clonal origin of cancer).
- The cell population at risk are the tissue pluripotent (stem) cells.
- Every time DNA replicates, permanent mistakes could occur.
- Carcinogenesis is a stochastic process.



# Where can chemicals influence carcinogenesis? DNA interaction & cell division



# Risk Factors for increasing numbers of DNA errors to increase probability of carcinogenic outcome

- Each stem cell division has a probability of mutation
- Probability of mutations which lead to cancer increased by:
  - R – Number of cell replications
  - H – Hereditary related errors
  - E – Environmental factors
    - $E_G$ – Environmental stressors  directly damaging the genome
    - $E_{IR}$ -  Environmental stressors inducing increased replication
- Scheme modified from Tomasetti and Vogelstein, 2015.

# Implications for 2 Year Bioassay

- Designed to maximize probability of neoplasms occurring
  - Maximum Tolerated Dose
  - Lifetime dosing
- Maximizes number of stem cell divisions
- Interplay of dose-limiting toxicity and toxicity leading to proliferation
- Overlay of probabilistic processes

*Proc. Natl. Acad. Sci. USA*
Vol. 87, pp. 7772–7776, October 1990
Medical Sciences

Long been concern about Rodent Bioassays

## Chemical carcinogenesis: Too many rodent carcinogens*

(tumor promotion/mutagenesis/mitogenesis/animal cancer tests)

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**ABSTRACT** The administration of chemicals at the maximum tolerated dose (MTD) in standard animal cancer tests is postulated to increase cell division (mitogenesis), which in turn increases rates of mutagenesis and thus carcinogenesis. The animal data are consistent with this mechanism, because a high proportion—about half—of all chemicals tested (whether natural or synthetic) are indeed rodent carcinogens. We conclude that at the low doses of most human exposures, where cell killing does not occur, the hazards to humans of rodent carcinogens may be much lower than is commonly assumed.

# Some Predictions and Outcomes for 2 Year Bioassay.

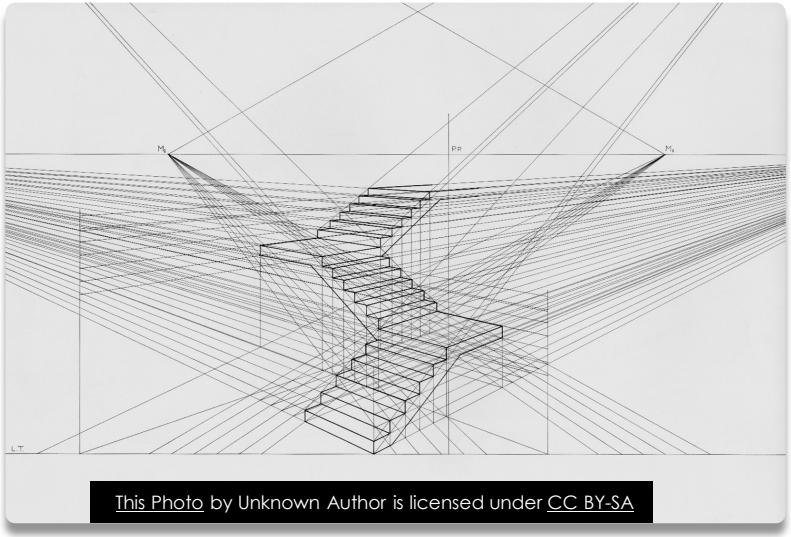
- Likely to be high proportion of "positives"
  - approx. 50%
- Likely to be variation in results
  - Only 57% correlation of studies with same chemical – *Gottman et al 2005*
- Likely to be correlation between toxicity and carcinogenicity
  - 90-day NOAEL and the tumour NOAEL similar - *Braakhuis et al 2018*
- Many ways to induce cell proliferation
  - Difficult to reproduce results with alternative assays – *Doktorova et al, 2014*

# 2 Year Bioassay Results; Consider Cancer Theory

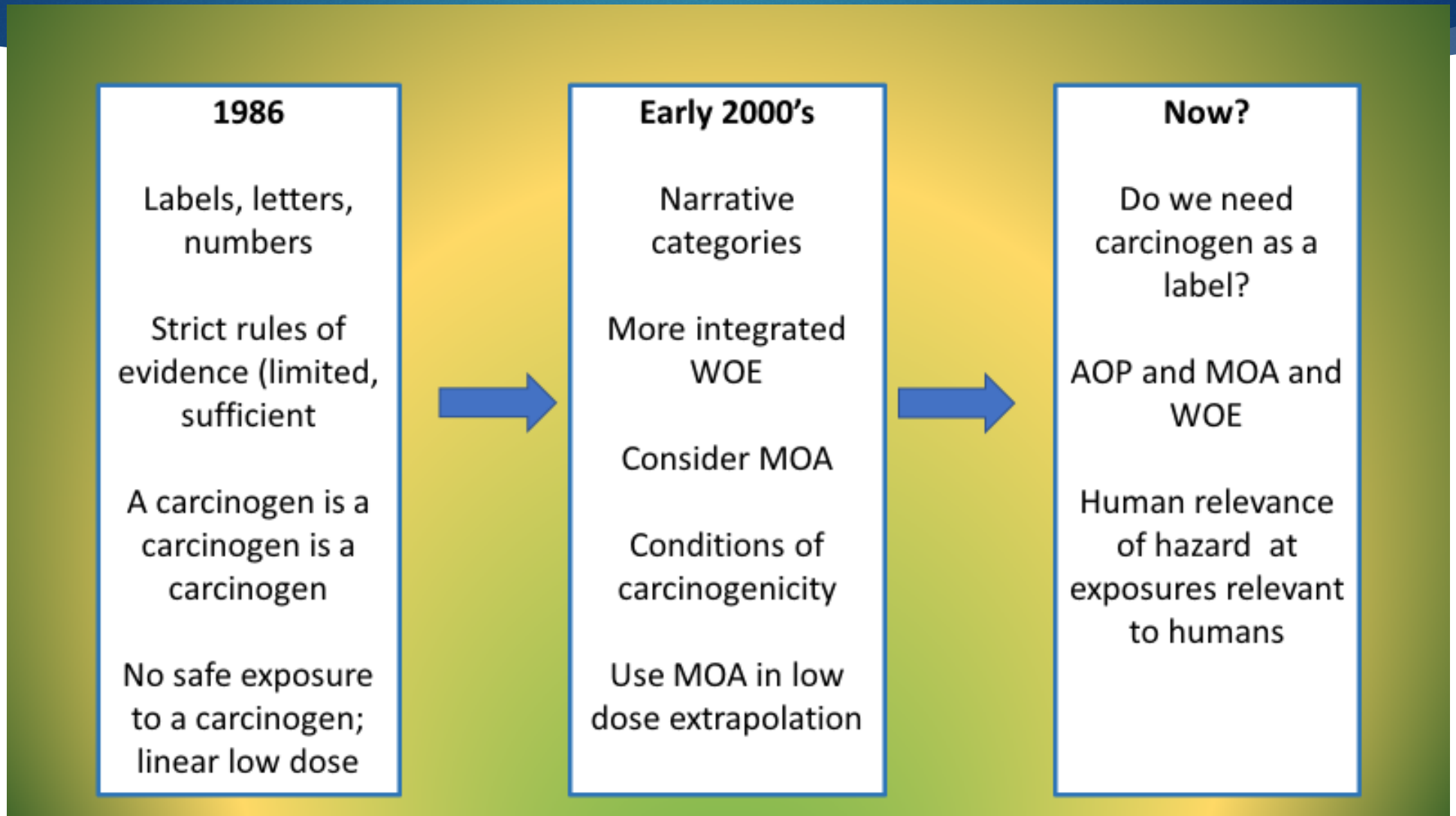
- More nuanced than simply "carcinogen or non-carcinogen".
  - *Tumors*: genotoxicity or cellular proliferation (receptor or non-specific) activity at doses equal to or lower than dose limiting toxicity
  - *No tumors*: no genotoxicity or cellular proliferation (receptor or non-specific) activity or only at doses higher than dose limiting toxicity

# Shift in Perspective
# Move from identifying "carcinogens" to assessing carcinogenic potential

- Function of dose level and duration of dosing required to cause neoplasia via responses such as genotoxicity, cytotoxicity and cell proliferation.
- The lower the dose level and the shorter the duration necessary of the higher the carcinogenic potential
- Exposure at levels and durations that do not increase those responses will not cause an increase in cancer.

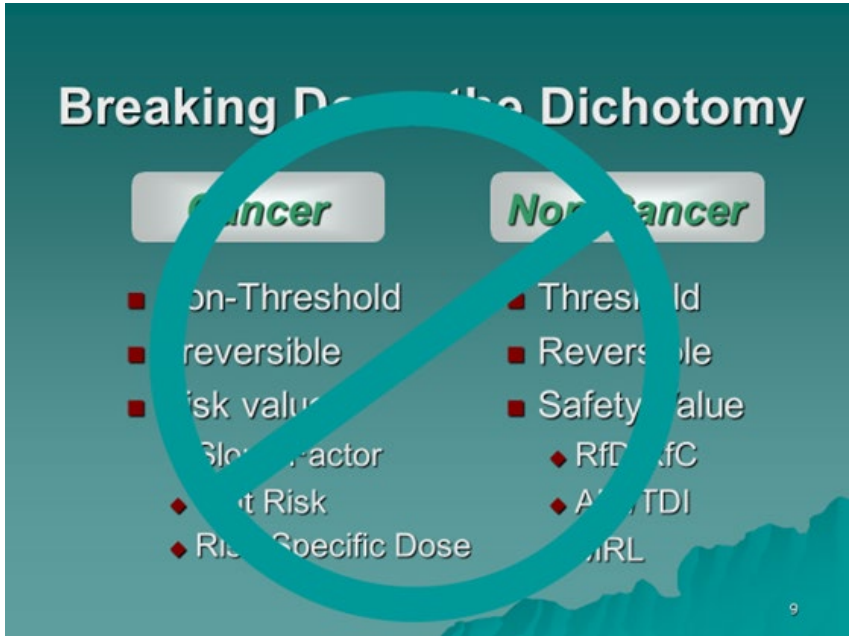


# Progress in Cancer Risk Asssessment



# Do We Need a Separate Category for Carcinogenicity?

- Identify and characterize genotoxicity
  - Can be included within Mutagenicity category for classification, risk assessment and risk management processes
- Identify and characterize toxicity which can lead directly or indirectly to increased cell division
  - Can be included within Toxicity category for classification, risk assessment and risk management processes



# EPA Does Not Have a Carcinogen List



October 2, 2014

**Chemicals Evaluated for Carcinogenic Potential**
**Office of Pesticide Programs**
**U.S. Environmental Protection Agency**

Labeling may pose its own hazard

**BACKGROUND**

**What is this list?**
The following list provides an overview of pesticide chemicals evaluated for carcinogenic potential by EPA's Pesticide Program through October 2012. The evaluation of many of these chemicals is an ongoing process. Therefore, the information in this list may be subject to change as new and/or additional data are submitted to EPA. This list will be updated annually.

**How should the information provided in this list be used?**
Although this list is available to the public, note that the list represents only the potential carcinogenicity hazard for the chemical with no consideration of exposure information. This list is not intended to be used independent of the full risk assessment for the chemical. When EPA completes a risk assessment on a pesticide, a variety of toxicity information, including potential for noncancer effects (e.g., neurotoxicity, developmental and reproductive toxicity, immunotoxicity, etc) and carcinogenicity, are considered in determining whether to register a pesticide and what requirements for use of the pesticide need to be in place to protect human health. The simple fact of being listed here does not imply that the pesticide poses a significant cancer hazard to the public from use

# Conclusions


- Cancer theory points us in certain directions
  - Theory describes carcinogenesis arising from multiple mutations in dividing stem cells
  - Chemicals can cause increase in neoplasia by direct action with DNA or by increasing cell divisions
  - Stochastic process – no bright line between carcinogen and non-carcinogen
- Rodent bioassay – theory would predict high number of positives, low reproducibility, relationship between toxicity and neoplasia
- Assess carcinogenic potential, not carcinogen or non-carcinogen
- Neoplasia an adverse outcome from Mutagenicity or Toxicity – Separate category not necessary
- Cancer classification has served a purpose, but now it is time to move on.

# Chemical Carcinogenicity Revisited 2: Current Knowledge of Carcinogenesis Shows that Categorization as a Carcinogen or Non-Carcinogen is Not Scientifically Credible - https://doi.org/10.1016/j.yrtph.2019.01.024

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