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Conflict of Interest Statement

I declare no financial interests related to the subject matter of my presentation.

Session 1 Science Topic

Liver tumor modes of action

The IARC Monographs Evaluations:
A Two-Step Process

Step 1: Categorize each line of evidence using defined terms

Cancer in humans

- *Sufficient evidence*
- *Limited evidence*
- *Inadequate evidence*
- *Evidence suggesting lack of carcinogenicity*

Cancer in experimental animals

- *Sufficient evidence*
- *Limited evidence*
- *Inadequate evidence*
- *Evidence suggesting lack of carcinogenicity*

Mechanistic and other relevant data

- *"Weak," "moderate," or "strong" evidence?*
- *Does this– or can it– occur in humans?*

Step 2: Integrate findings in overall evaluations

Overall evaluation

- Group 1 *Carcinogenic to humans (118)*
- Group 2A *Probably carcinogenic to humans (80)*
- Group 2B *Possibly carcinogenic to humans (289)*
- Group 3 *Not classifiable as to its carcinogenicity to humans (502)*
- Group 4 *Probably not carcinogenic to humans (1)*

Evaluating Mechanistic and Other Relevant Data

Cancer in humans	Cancer in experimental animals	Mechanistic and other relevant data — Preamble Part B, Section 6(c)

- Are the mechanistic data “weak,” “moderate,” or “strong”?

Have the mechanistic events been established? Are there consistent results in different experimental systems? Is the overall database coherent?

Has each mechanism been challenged experimentally? Do studies demonstrate that suppression of key mechanistic processes leads to suppression of tumour development?

- Is the mechanism likely to be operative in humans?

Are there alternative explanations? Could different mechanisms operate in different dose ranges, in humans and experimental animals, or in a susceptible group?

Note: an uneven level of support for different mechanisms may reflect only the resources focused on each one

Mechanistic Data: Challenges

IARC Monographs
Volume 100
International Agency for Research on Cancer
World Health Organization

- Different human carcinogens may operate through distinct mechanisms
- Many human carcinogens act via multiple mechanisms
- There is no broadly accepted, systematic method for evaluating mechanistic data to support cancer hazard identification

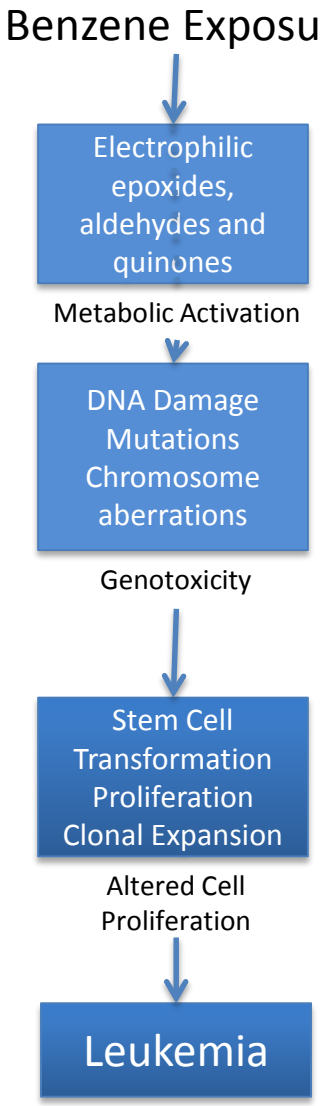
10 Key Characteristics of Human Carcinogens

Key characteristic:
1. Is Electrophilic or can be metabolically activated
2. Is Genotoxic
3. Alters DNA repair or causes genomic instability
4. Induces epigenetic alterations
5. Induces oxidative stress
6. Induces chronic inflammation
7. Is immunosuppressive
8. Modulates receptor-mediated effects
9. Causes immortalization
10. Alters cell proliferation, cell death, or nutrient supply

- **Established human carcinogens** commonly exhibit one or more of these characteristics
- Evidence of these characteristics, especially in humans or as intermediate biomarkers in human specimens can **provide biological plausibility** for epidemiological findings and/or early warning if no epidemiology exists

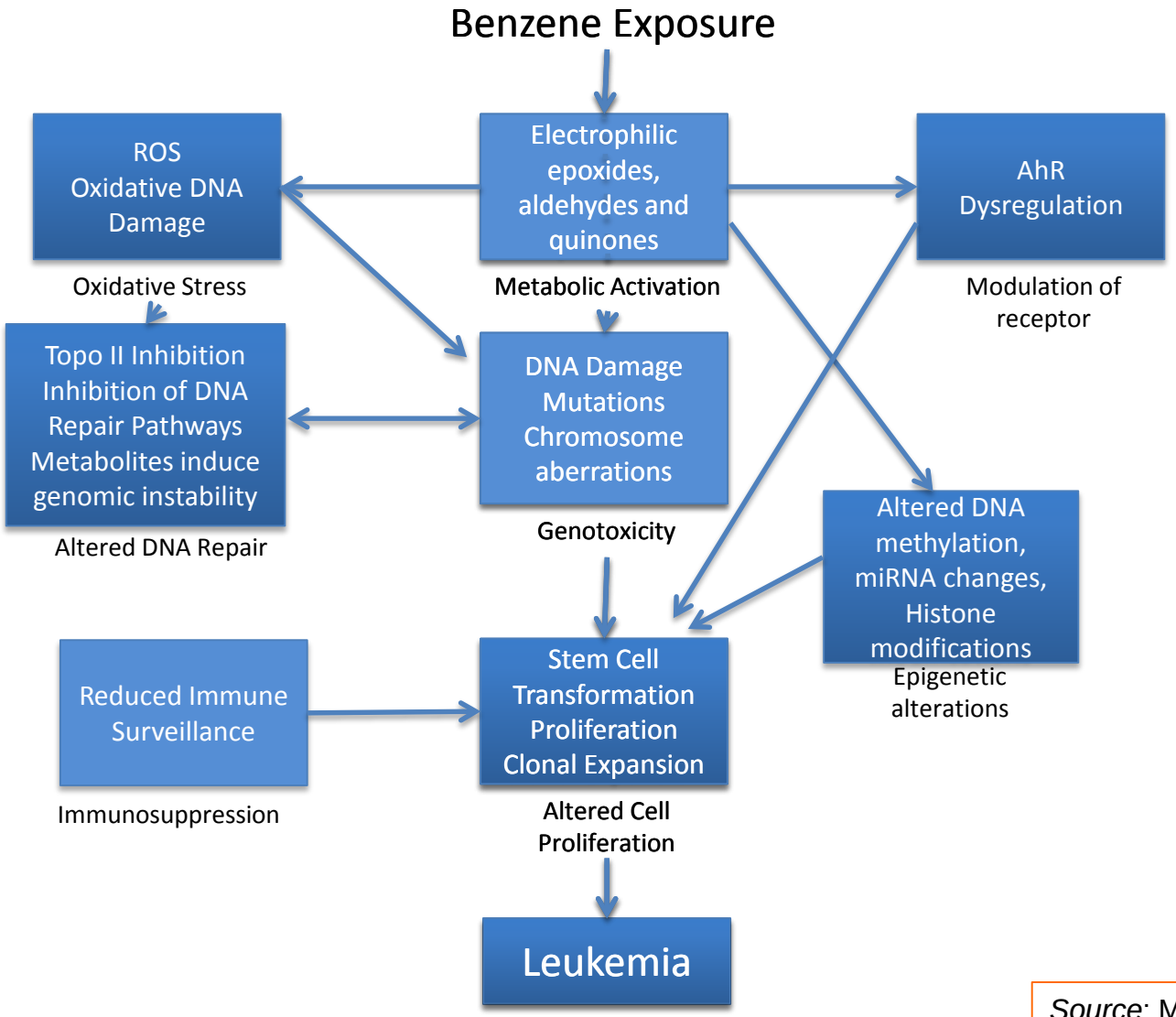
Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, DeMarini DM, Caldwell JC, Kavlock RJ, Lambert P, Hecht SS, Bucher JR, Stewart BW, Baan R, Cogliano VJ and K Straif. *Env Health Persp.*, *124(6):713-21*

Key Characteristics of Benzene: An Adverse Outcome Pathway?



Source: MT Smith

An Adverse Outcome Network Involving 8 Key Characteristics



Source: MT Smith