Chemical Carcinogenicity Revisited

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Risk Assessment Specialty Section Webinar
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Chemical Carcinogenicity Revisited

- Wolf, D.C., Cohen, S.M., Boobis, A.R., Dellarco, V.L., Fenner-Crisp, P.A., Moretto, A., Pastoor, T.P., Schoeny, R.S., Seed, J.G., Doe, J.E. 2019. Chemical carcinogenicity revisited 1: A unified theory of carcinogenicity based on contemporary knowledge. Regul Toxicol Pharmacol. 103:86-92.

- Doe, J.E., Boobis, A.R., Dellarco, V., Fenner-Crisp, P.A., Moretto, A., Pastoor, T.P., Schoeny, R.S., Seed, J.G., Wolf, D.C. 2019. Chemical carcinogenicity revisited 2. Current knowledge of carcinogenesis shows that categorization as a carcinogen or non-carcinogen is not scientifically credible. Regul Toxicol Pharmacol. 103:124-129

- Cohen, S.M., Boobis, A.R., Dellarco, V.L., Doe, J.E., Fenner-Crisp, P.A., Moretto, A., Pastoor, T.P., Schoeny, R.S., Seed, J.G., Wolf, D.C. 2019. Chemical carcinogenicity revisited 3: Risk assessment of carcinogenic potential based on the current state of knowledge of carcinogenesis in humans. Regul Toxicol Pharmacol. 103:100-105

Order of Presentation

- A unified theory of carcinogenicity based on contemporary knowledge– Dr. Fenner–Crisp

- Current knowledge of carcinogenesis shows that
- categorization as a carcinogen or non-carcinogen is not scientifically credible – Dr. Schoeny

- Risk assessment of carcinogenic potential based on the current state of knowledge of carcinogenesis in humans– Dr. Cohen

A unified theory of carcinogenicity based on contemporary knowledge

What is our current understanding of the phenomenon we define as "carcinogenesis?"

How should we interpret and apply this understanding in the context of characterizing the carcinogenic potential of agents to which we are exposed in our environment?

Does the current Framework for researching, testing, analyzing, assessing, classifying, labelling and managing known or hypothesized hazard and risk for this endpoint of concern represent the most scientifically-sound approach to protection of the public health?

Carcinogenesis

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).

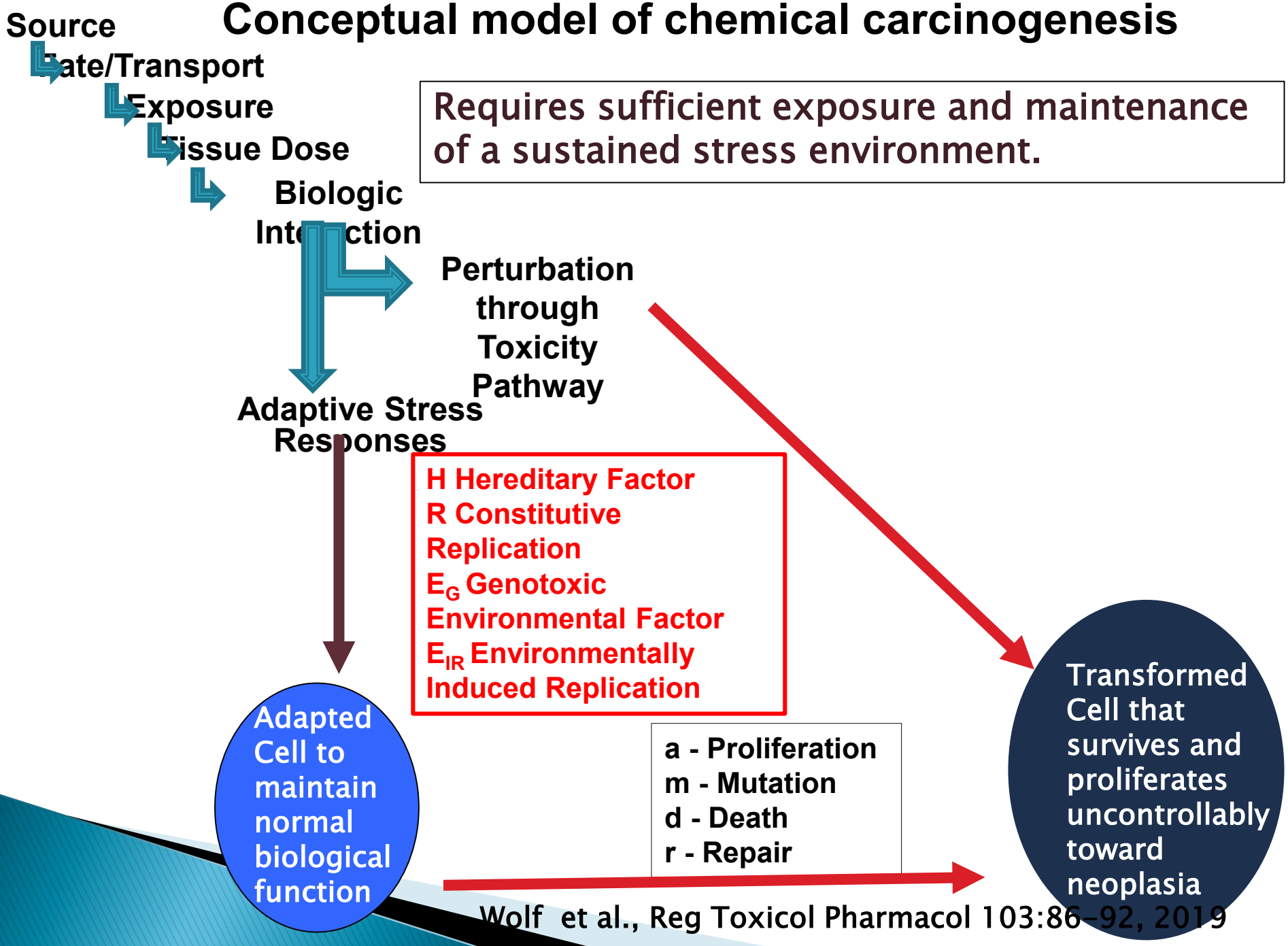
The cell populations at risk are the tissue pluripotent (stem) cells.

Every time DNA replicates, permanent mistakes can occur.

Carcinogenesis is a stochastic process.

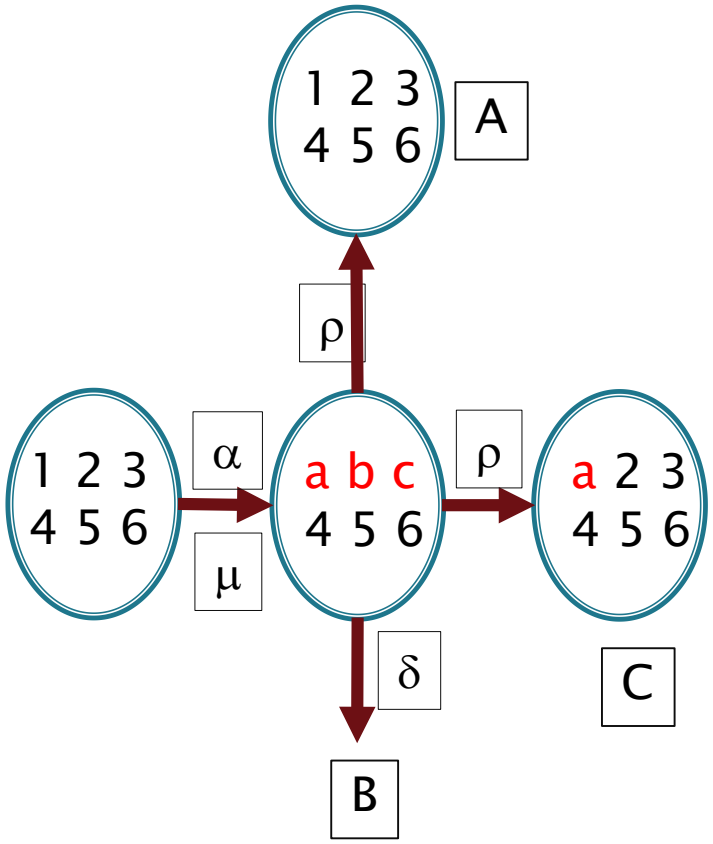
Doe et al., Reg Tox Pharm 103:124-129, 2019

Conceptual model of chemical carcinogenesis



Wolf et al., Reg Toxicol Pharmacol 103:86–92, 2019

First step toward initiation of a somatic cell

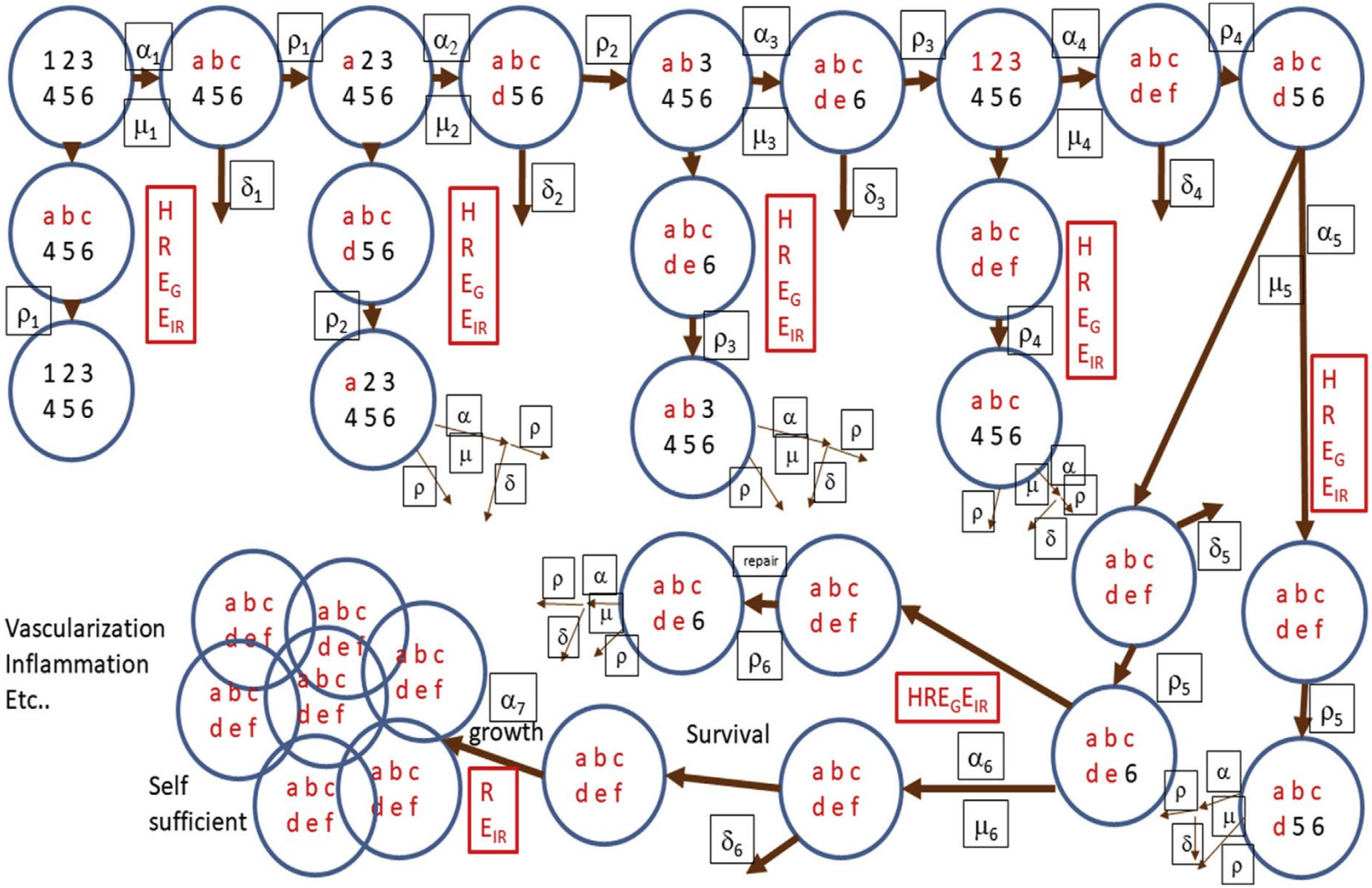


The parent cell divides (α) and has a risk of mutation (μ, small case letters) to occur.

These mutations may be repaired (ρ) or one or more may be of such significance that they induce the cell to die (δ).

The outcome of this could be a daughter cell that is a clone of the parent (A), a dead cell (B) because the mutation(s) was(were) not compatible with a functional life, or a daughter cell that contains a mutated gene (C).

Wolf et al., Reg Toxicol Pharmacol 103:86-92, 2019



The integration of drivers of mutational events leading to a fully initiated cell

Source

Fate/Transport

Exposure

Tissue Dose

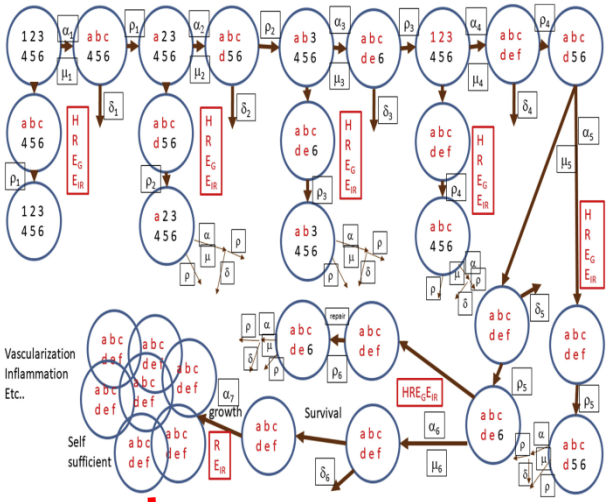
Biologic Interaction

Perturbation through Toxicity Pathway

Adaptive Stress Responses

Population model of chemical carcinogenesis. Requires sufficient exposure and maintenance of a sustained stress environment.

H Hereditary Factor
R Constitutive Replication
E_G Genotoxic Environmental Factor
E_{IR} Environmentally Induced Replication



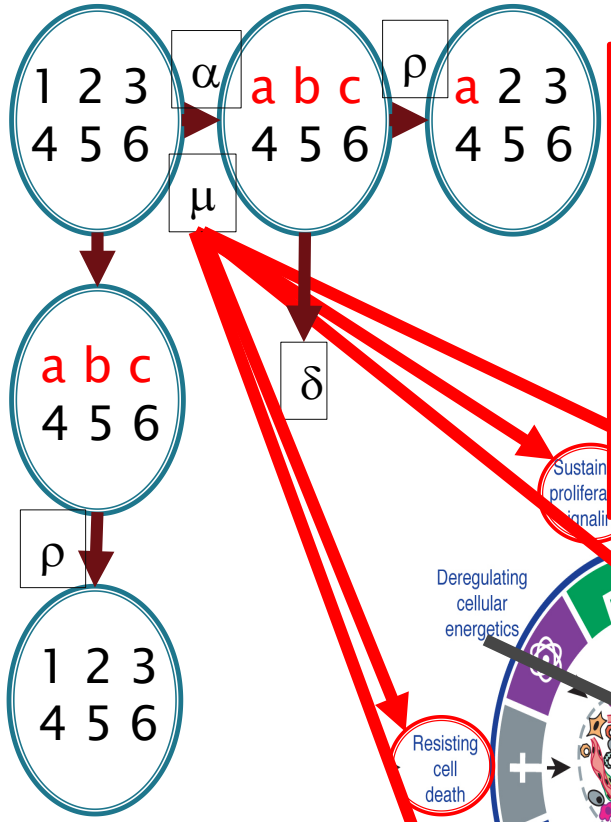
Adapted Cell to maintain normal biological function

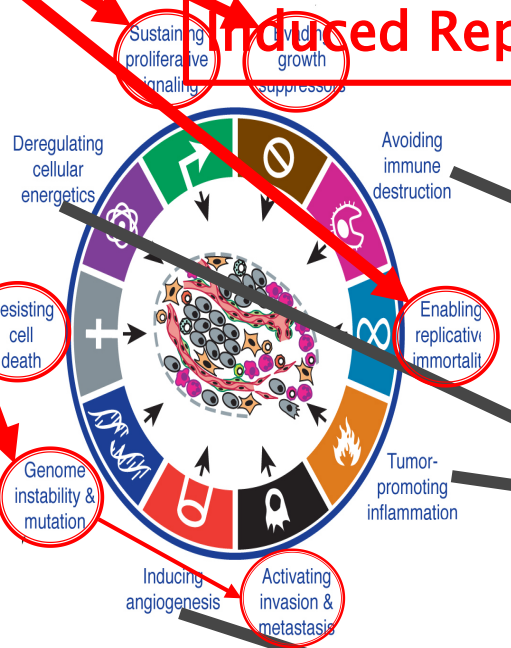
α – Proliferation
μ – Mutation
δ – Death
ρ – Repair

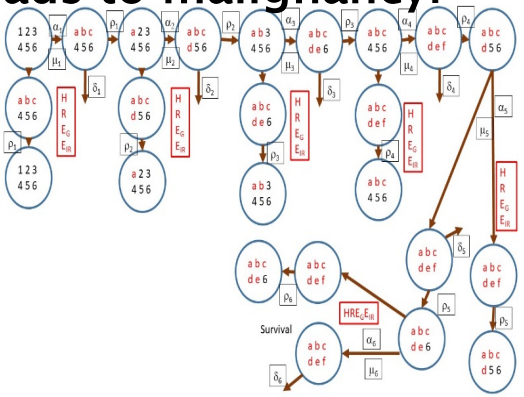
Wolf et al., Reg Toxicol Pharmacol 103:86–92, 2019

H Hereditary Factor
R Constitutive Replication
E_G Genotoxic Environmental Factor
E_{IR} Environmentally Induced Replication

In response to the sustained stress environment, the hyperplasia continues to accumulate the capabilities that enable it to survive and through replication leads to malignancy.







growth

Malignancy

R
E_{IR}

R
E_{IR}

Hanahan and Weinberg, 2011

Cell PRESS

Question: Does the current Framework for researching, testing, analyzing, assessing, classifying, labelling and managing known or hypothesized hazard and risk for this endpoint of concern represent the most scientifically-supportable approach to protection of the public health?

Answer:
A resounding "No!"