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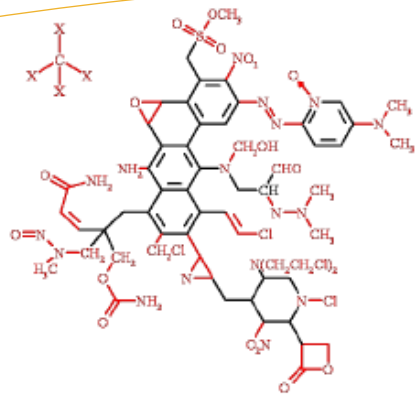
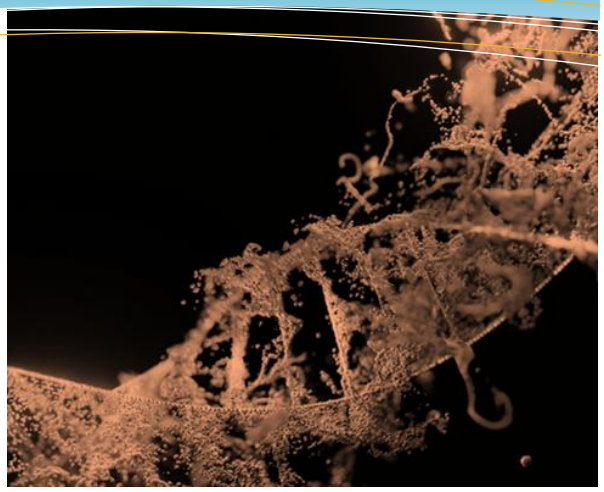
GERMAN SOCIETY OF
TOXICOLOGY

Poison of the month



„Ashby-Tennant Supermutagen“



The proposal to select the “Supermutagen” as the Toxin of the Month originated from the Working Group of Computational Toxicology…

…as this concept exemplifies the transition from classical, empirical toxicology to modern, computer-based approaches. Ashby and Tennant’s theoretical model is regarded as an early blueprint for today’s QSAR and in-silico methods, which have become indispensable in regulatory and research settings. With this choice, the working group seeks to highlight the historical significance of the concept while underscoring the relevance of contemporary computational modelling for a faster, more precise, and animal-reduced risk assessment.

Mutagenicity is not the same as Carcinogenicity

Mutagenicity refers to a substance’s ability to induce genetic mutations, typically through direct DNA damage. **Carcinogenicity**, by contrast, describes the ability to cause cancer in an organism, a process that often involves mutations but may also arise from **hormonal effects, chronic inflammation, or oxidative stress**.

Thus, not every mutagenic substance is carcinogenic, and not every carcinogen is mutagenic. Both cases can be found in the NTP data analyzed by Ashby and Tennant: **hydroquinone** produced renal tumours without mutagenicity,

The Supermutagen – The Most Dangerous Molecule Never Made

The question of whether the carcinogenic potential of a chemical can be inferred from its structure has long occupied toxicological research. The study of chemical carcinogenesis began with the polycyclic aromatic hydrocarbon benzo[a]pyrene, a component of tar and tobacco smoke, first isolated from coal tar in 1837 by the French chemist Auguste Laurent. It was among the first substances shown to cause cancer through specific structural features. Later, it was discovered that benzo[a]pyrene undergoes enzymatic oxidation to highly reactive epoxides capable of forming DNA adducts and inducing mutations, a pivotal insight that certain functional groups can serve as structural warning signals for genotoxic potential.

Building on this foundation, John Ashby and Raymond Tennant developed their concept in the early 1990s. They evaluated 301 chemicals tested by the U.S. National Toxicology Program (NTP), collecting for each compound tumour findings in rats and mice, results from the bacterial Ames mutagenicity assay, and the presence of DNA-reactive structural alerts. This integrative approach allowed the relationships between chemical structure, mutagenicity, and carcinogenicity to be visualized systematically.

Electrophilic groups such as epoxides, nitro compounds, or aromatic amines can react with DNA bases and induce mutations. Ashby and Tennant compiled such substructures into a conceptual “building-block system” and integrated them into the hypothetical “Supermutagen”, a theoretical molecule encompassing all known structural alerts. With each new observation, the model was expanded, for example, by adding the aliphatic nitro group after tetranitromethane had been confirmed as a

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whereas allyl glycidyl ether was strongly mutagenic but caused only minimal tumour incidences. This distinction remains fundamental to toxicological risk evaluation today.

Supermutagen – a Thought Experiment

A molecule combining all DNA-reactive groups, as envisioned in the Supermutagen, would be chemically almost impossible to realize. Reactive moieties such as epoxides, nitro groups, or alkylating units would become unstable, or decompose through side reactions long before they could act in biological systems.

The significance of the Supermutagen therefore does not lie in its synthetic feasibility but in its symbolic condensation of all known structural alerts. It serves as a didactic construct, illustrating which functional groups act as warning signals for DNA reactivity and how their combination can potentiate genotoxic risk. In practice, it remains a conceptual model yet, one that has profoundly shaped the development of modern predictive approaches and the ongoing discussion about the limits of structure-based toxicology.

potent lung carcinogen.

The concept offered a clear logic: the more structural alerts a molecule possesses, the higher its likelihood of being a genotoxic carcinogen. Combined with mutagenicity tests such as the Ames assay, this framework enabled early assessment of potential cancer risks.

Ashby and Tennant, however, also recognized the limitations of their system. Not all chemicals bearing structural alerts proved carcinogenic, and some carcinogens showed neither mutagenicity nor any obvious structural alert. For instance, hydroquinone, an antioxidant used in plastics and formerly as a photographic developer, induced renal tumours despite being non-mutagenic in bacterial tests. Conversely, allyl glycidyl ether, a monomer for epoxy resins and coatings, was strongly mutagenic yet produced only a very low tumour incidence in mice. These examples highlighted the importance of bioavailability, metabolism, organ specificity, and alternative mechanisms in modulating carcinogenic outcomes.

The structural alert concept profoundly influenced toxicological practice. It solidified the importance of identifying structural features related to toxicity, paving the way for modern predictive methods. Even today, together with modern QSAR (Quantitative Structure–Activity Relationship) models, it is still a cornerstone of structure-based toxicological prediction.

Using large databases and advanced algorithms, molecular properties are now translated into predictions, for example, to identify DNA-reactive potential.

By integrating electronic, lipophilicity, solubility, and stability parameters, together with machine learning, QSAR models capture complex interdependencies and embed them into comprehensive evaluation frameworks. They allow early identification and prioritization of substances with high mutagenic potential, are gaining increasing regulatory acceptance, and contribute substantially to the reduction of animal testing in chemical safety assessment.

By Ute Haßmann

Literature and links:

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