

## Thresholds for carcinogens.

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Accepted on 04 June, 2021

### Editorial

A carcinogen is a chemical or agent that has the potential to cause cancer. Non-genotoxic carcinogens and genotoxic carcinogens are two types of carcinogens. The level of exposure below which there is no risk of cancer is known as the threshold. Any substance, radionuclide, or radiation that promotes carcinogenesis, or the production of cancer, is referred to as a carcinogen. This could be owing to the potential to harm the genome or to cellular metabolic processes being disrupted. Several radioactive compounds are carcinogens, but their cancer-causing properties are related to the radiation they emit, such as gamma rays and alpha particles. Any condition in which normal cells are damaged and do not die as quickly as they divide via mitosis is known as cancer. Carcinogens may raise the risk of cancer by modifying cellular metabolism or directly destroying DNA in cells, interfering with biological processes and causing uncontrolled, malignant cell division, eventually leading to tumour formation.

For non-genotoxic carcinogens, there is generally agreement that a threshold exists. The linear no-threshold (LNT) model, which theoretically calculates cancer risks occurring after low doses of carcinogens by linearly projecting downward from experimentally determined risks at high doses, is the basis for current regulatory cancer risk assessment concepts and methods. The two-year rodent bioassays are used to determine the high-dose cancer risks in animals and then extrapolate the number of carcinogen-induced tumours (tumour incidence) that will occur during the lifetimes of humans exposed to environmental carcinogens at doses that are typically orders of magnitude lower than those used in the rodent assays. An integrated toxicological study is performed here to examine tumour latency as an alternate and once-promising method for evaluating carcinogen-induced cancer risks at low doses. Tumour latency, rather than tumour incidence, describes the time it takes for a tumour to develop after exposure to a carcinogen. The evidence for and against carcinogen-induced tumour latency is provided, debated, and examined in connection to dosage, dose rates, and the dose-related concepts of initiation, tumour promotion, tumour regression, tumour incidence, and hormesis. Extensive experimental evidence suggests

Tumour latency (time to tumour) is inversely related to carcinogen dose, and

Lower carcinogen doses have quantifiably discrete latency thresholds below which tumour promotion, progression, and growth are delayed or avoided within a normal lifespan.

Such latency limits not only fit well with the concept of tumour promotion, but they also fit well with the existence of tumour incidence thresholds, stochastic tumour start processes, and hormesis compensatory repair mechanisms. Most crucially, these research and arguments establish good theoretical, experimental, and mechanistic rationales for revisiting the underlying premises of low-dose linearity and upgrading current cancer risk assessment techniques to include the concept of carcinogen thresholds. While it is widely believed that genotoxic carcinogens have no dose threshold for their carcinogenic potential, there is mounting evidence that even very low doses are incapable of causing tumours or preneoplastic lesions. Thus, not only so-called epigenetic 'non-genotoxic' chemicals such as phenobarbital and benzene hexachloride, but also unmistakably genotoxic carcinogens such as the heterocyclic amines 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline and amino-1-methyl-6-phenylimidazo[4,5-b]pyridine, and the nitro may have a realistic dosage threshold below which no histopathologically detectable lesions occur. In response to low dosages of all sorts of DNA-damaging chemicals, some form of physiological adaptation is likely to occur. At very low doses, 'non-genotoxic' substances may produce hormesis, or paradoxical protection. While it is widely believed that genotoxic carcinogens have no dose threshold for their carcinogenic potential, there is mounting evidence that even very low doses are incapable of causing tumours or preneoplastic lesions.

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**Citation:** Markiewicz M. Thresholds for carcinogens. *Allied J Med Res.* 2021;5(S3):11