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Mini Review

Reconsidering the scientific validity of the term "non-toxic" in toxicological risk assessment

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Abstract

The term "non-toxic" is widely used in consumer product labeling despite the absence of a formal scientific or regulatory definition. Contemporary toxicology recognizes that adverse biological effects depend on dose, duration of exposure, route of entry, genetic variability, and underlying molecular mechanisms. This review critically examines the scientific limitations of the term "non-toxic," with particular emphasis on chronic toxicity, genotoxic mechanisms, and carcinogenic processes. Evaluation of toxicological principles and regulatory practices indicates that the term is incompatible with current scientific understanding and may undermine accurate risk communication.

Keywords: Toxicology, Dose–response assessment, Genotoxicity, Carcinogenesis, Chemical risk, Consumer labeling

Introduction

The principle that toxic effects depend on the quantity of exposure has been recognized since the sixteenth-century work of Paracelsus [1]. This concept remains a cornerstone of toxicology and underpins modern frameworks for hazard identification and risk assessment [2,3]. Despite this foundational understanding, the term "non-toxic" continues to appear in product labeling and marketing, often implying unconditional safety.

Such terminology conflicts with contemporary toxicological knowledge. Adverse effects result from complex interactions among chemical properties, biological systems, and exposure conditions, rather than from absolute classifications of substances as safe or unsafe. This review evaluates the scientific credibility of the term "non-toxic" and highlights its limitations in the context of chronic exposure, genomic damage, and the multistage nature of carcinogenesis.

Dose–Response Relationships and Biological Variability

Biological responses to chemical exposure typically follow graded dose–response relationships. At sufficiently low exposure levels, observable adverse effects may be absent or fall below detection thresholds, whereas increasing doses can produce progressive biochemical disruption, tissue injury, organ dysfunction, and, in extreme cases, mortality [2,4]. In a recent study, higher levels of cotinine (a marker of exposure to nicotine) were associated with earlier menopause and shorter reproductive lifespan, with dose-dependent effects that were strongest at higher exposures and in vulnerable subgroups of women [5]. This paradigm applies broadly across chemical classes, including endogenous compounds, pharmaceuticals, and environmental agents.

However, dose–response relationships may be altered under conditions of prolonged or repeated exposure, co-exposure to other chemicals, or for substances with specific mechanisms of action, such as genotoxic carcinogens, for which clear thresholds may not exist. In addition, susceptibility to toxicity varies widely among individuals and populations due to factors such as age, sex, nutritional status, disease state, and genetic polymorphisms [2,3,6,7]. Consequently, a substance that produces minimal effects in one biological system or population may elicit significant adverse effects in another, rendering categorical descriptors such as "non-toxic" scientifically imprecise.

Constraints of Traditional Toxicity Endpoints

Conventional toxicity metrics, including the median lethal dose (LD_{50}), illustrate the limitations of traditional hazard assessment. LD_{50} values are highly dependent on experimental variables such as species, strain, formulation, and route of exposure, leading to substantial inter-study variability [2,4]. Moreover, these endpoints primarily reflect acute lethality and provide limited insight into subchronic or chronic toxicity.

Long-term adverse outcomes—including endocrine disruption, neurodevelopmental impairment, and carcinogenesis—may occur at exposure levels far below those associated with acute toxicity [3]. The combined effects of multiple chemicals acting on different molecular and physiological pathways may further contribute to toxic or carcinogenic synergy [8]. Reliance solely on short-term toxicity endpoints is therefore insufficient for comprehensive risk evaluation.

Influence of Exposure Route and Chemical Properties

The route of exposure strongly influences both the magnitude and nature of toxic effects [9]. Differences in absorption, metabolic activation, distribution, and elimination can result in marked variations in toxicity for identical doses administered via inhalation, ingestion, or dermal contact [2,9,10]. A recent study suggests that the effective concentration and chemical activity of a substance may differ across environmental matrices, reflecting medium-dependent changes in solubility, speciation, and colloidal behavior that govern its physicochemical form and potential bioavailability [11]. Differences approaching an order of magnitude have been reported depending on the exposure pathway [4].

Physicochemical properties such as solubility, volatility, particle size, and chemical speciation further affect bioavailability and toxicokinetic behavior [3]. These factors complicate efforts to assign universal safety labels to chemical substances.

Genotoxic Effects and Multistage Carcinogenesis

Many chemicals exert adverse effects at the genomic level without producing immediate overt toxicity. Genotoxic agents can induce DNA damage directly or indirectly, cause chromosomal alterations, or disrupt epigenetic regulation, thereby increasing mutational burden. Environmental carcinogens may promote tumorigenesis by enhancing endogenous mutagenic processes rather than initiating distinct mutations [12]. Such effects can remain clinically silent for extended periods.

Cancer is a multistep process driven by the progressive accumulation of genetic and epigenetic alterations over time [13,14]. Data from our laboratory and others demonstrate that genotoxic exposures can disrupt DNA repair pathways [15,16], thereby promoting genomic instability [16]. We have further shown that aberrant overexpression of DNA repair and cell-cycle regulators, including APE1 and TTK, compromises genome integrity and contributes to chemoresistance [17,18] and tumorigenesis [18]. Notably, functional interactions between dysregulated repair and checkpoint pathways (e.g., APE1–TTK) further exacerbate genomic instability and proliferative signaling (unpublished data). For many carcinogens, risk is driven primarily by prolonged, repeated exposure rather than acute high-dose events. Persistent DNA damage, impaired repair mechanisms, and selective clonal expansion contribute to malignant transformation [13]. Importantly, many genotoxic carcinogens lack a clearly defined exposure threshold below which cancer risk can be assumed to be absent [19]. Several recent studies indicate that prolonged exposure to carcinogens, even at doses considered low or within regulatory limits, can cumulatively enhance mutagenic events and promote tumor development over time [20–22]. Accordingly, regulatory approaches generally assume that no level of exposure to genotoxic carcinogens is entirely without risk [23], further undermining the scientific validity of the term "non-toxic."

Implications for Regulation and Risk Communication

Regulatory frameworks worldwide emphasize exposure-based risk assessment rather than absolute safety classifications. While hazardous substances are formally identified and regulated, no major regulatory authority endorses or requires the designation "non-toxic." This reflects the recognition that chemical safety is inherently conditional and context dependent.

Use of the term "non-toxic" may obscure scientific uncertainty and foster unrealistic perceptions of safety, particularly among vulnerable populations such as children or genetically predisposed individuals. Effective risk communication should instead emphasize exposure conditions, susceptibility, and long-term health risks, including genotoxic and carcinogenic outcomes.

Conclusion

Current toxicological science does not support the classification of any substance as inherently "non-toxic." Adverse effects depend not only on dose but also on exposure duration, route of entry, biological susceptibility, and underlying molecular mechanisms, including those leading to genomic damage and cancer. As understanding of chronic and low-dose effects continues to evolve, reliance on absolute safety terminology becomes increasingly problematic. The term "non-toxic" is therefore scientifically imprecise and may contribute to misleading risk perceptions in both regulatory and consumer contexts.

Conflict of Interest

The authors declare no conflict of interest.

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