Achieving Clarity in CMR Definition and Classification: Working Towards a Consolidated Framework

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79th TSRC Sept 2026

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INTRODUCTION

Next generation tobacco products (NGP) should exclude carcinogens, mutagens, reprotoxic ingredients (CMRs), in line with manufacturers' duty of care and applicable jurisdictional regulatory requirements. The development of compliant products depends on robust definitions and classifications for CMRs. Because criteria vary slightly across regions and data sources, classifications can become inconsistent even for the same chemical. Drawing on a robust review of multiple authoritative sources - including regulatory frameworks, international guidelines, and scientific literature - this study proposes consensus CMR definitions and classification criteria that aim to reconcile the differences found across those sources.

METHODOLOGY

Our matrix follows three general steps (Figure 1). Consensus definitions and tier classifications were established from searches in authoritative sources such as US EPA, US FDA Center for Tobacco Products (FDA CTP), IARC, EU REACH, ECHA, DFG, EFSA, NTP, OSHA, Cal-OEHHA, ICH Guidelines, ATSDR, JECFA, WHO and OECD SIDS. Sources were evaluated and ranked according to criteria proposed by Bernal and Neilson (2021) (Table 1). Only top-ranking sources (Tier 1-2) were selected for developing consensus CMR definitions and a classification tier system. CMR consensus definitions were built using top authoritative sources, aided by AI and edited manually, The tier classification system also leveraged ad-hoc position papers on weight of evidence assessment (e.g. Dearfield et al., 2002, Brusick et al., 2016). A decision workflow was developed to determine tier assignments.

Figure 1. Overview of Consensus Definition Methodology

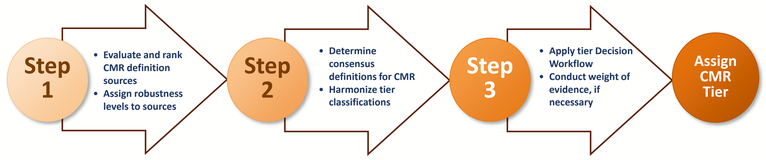


Table 1. Robustness/Ranking of Weight of Evidence Sources

Criterion Area	Robustness Level			
	1	2	3	4
Region	International or National	International or National	Any	Any
Expert Committee	Appropriate specialists; transparent member make up/ affiliations	Appropriate specialists; transparent member make up/ affiliations	Appropriate specialists; transparent member make up/affiliations	Not always transparent
Defined Classification for Health Endpoint	Tiered, discrete classifications and definitions	No classification; may depend on Level 1 source; definition may or may not be provided	No classification; definition may or may not be provided	No classification, or self-reported; definition may or may not be provided
Data Collection	Principles of systematic review (i.e. PRISMA)	Limited systematic review	Collated	Collated
Data Evaluation and Review Process	Multistep, peer-reviewed process	Multistep or peer-reviewed; often incorporates public engagement	Typically multistep; may not be peer-reviewed	Steps unclear; may not be peer reviewed and may be based on self-classification
Examples	US EPA, REACH, DFG,…	NTP, OEHHA,…	RIFM, EFSA,..	ECHA self-classification

The tier classification and definitions are proposed as a consensus interpretation of hazard classifications and weight-of-evidence determinations reported across the authoritative sources included in this review. For example, Table 2 presents the genotoxicity definitions and classifications identified from five authoritative sources.

Table 2 Genotoxicity Definitions and Classifications from Five Robustness Level 1

	Definition	Classification
US EPA	Genotoxicity pertains to all types of DNA damage (including mutagenicity).	Tier 1 - Human Mutagen Tier 2 – Probable Human Mutagen Tier 3 – Possible Human Mutagen Tier 4 – Not Classified
FDA CTP	Chemicals that induce adverse effects (e.g., DNA damage) on genetic components through a variety of mechanisms. (FDA CDER definition: Any deleterious change in the genetic material regardless of the mechanism by which the change is induced.)	FDA CTP only classifies substances for carcinogenicity with somatic genotoxicity supporting the classification for carcinogenicity. Tier 1 - Carcinogenic to Humans Tier 2 - Likely to Be Carcinogenic to Humans Tier 3 - Suggestive Evidence of Carcinogenic Potential Tier 4 - Potential Carcinogenic Hazard Tier 5 - Unlikely to Contribute to Carcinogenic Risk
IARC	Genotoxicity is the ability of substances to damage the genetic information within a cell, causing mutations, which may lead to cancer.	IARC only classifies substances for carcinogenicity with genotoxicity supporting the classification. Group 1 - Carcinogenic to Humans Group 2A - Probably Carcinogenic to Humans Group 2B - Possibly Carcinogenic to Humans Group C - Not Classifiable as to its Carcinogenicity to Humans
REACH/ ECHA	The terms 'genotoxic' and 'genotoxicity' apply to agents or processes which alter the structure, information content, or segregation of DNA.	ECHA only classifies substances for germ cell mutagenicity. Somatic mutagens are accounted for as part of ECHA classification of carcinogens. Group 1A – Know human germ cell mutagen Group 1B - Presumed to be potential gem cell mutagen in humans based on in vivo evidence Group 2 – Suspected human germ cell mutagen (often based on evidence of somatic mutagenicity or in vitro germ cell mutagenicity)
DFG	"Germ cell mutagenicity" refers specifically to mutagenicity in male and female germ cells and is distinguished from mutagenicity in somatic cells which can initiate cancer.	DFG only classifies substances for germ cell mutagenicity. Somatic mutagens are accounted for as part of DFG classification of carcinogens. Category 1 - Known human germ cell mutagen Category 2 - Known Mammal germ cell mutagen in vivo Category 3A & B - Mutagen in germ cells & suspected germ cell mutagen Category 4 – Not applicable Category 5 - Known germ cell mutagen, but a threshold can be established

RESULTS

Figure 2. Consensus CMR Definitions

Carcinogens: Substances[1], chemicals, or agents[2] capable of causing or reasonably anticipated to cause cancer in humans.

Developmental and Reproductive Toxicants[3]: Substances, chemicals, or agents capable of causing or reasonably anticipated to cause adverse effects on human reproduction or development.

Genotoxicants (including mutagens): Substances, chemicals or agents that can cause damage to the genetic material within a cell which may contribute to cancer and other genetic disorders such as developmental or heritable adverse effects.

[1]A form of matter that has a constant chemical composition and characteristic properties
[2] A substance or factor that produces, or is capable of producing, an effect
[3] Also referred to as DART for 'developmental and reproductive toxicity'

The strength of the evidence supporting a CMR hazard identification can vary. Thus, it is proposed to further consolidate the definition under a tiered classifications system which is harmonized from all the authoritative sources examined (Figure 3). Figure 4 describes a decision workflow for Tier classification determination.

Figure 3. Tier Classification Matrix for Carcinogenicity, Genotoxicity, and DART

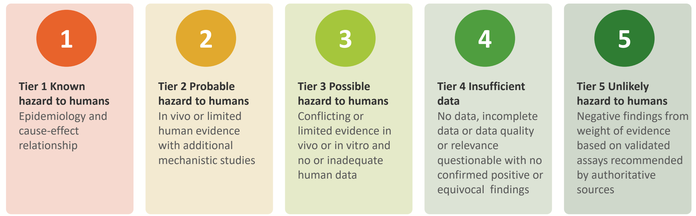
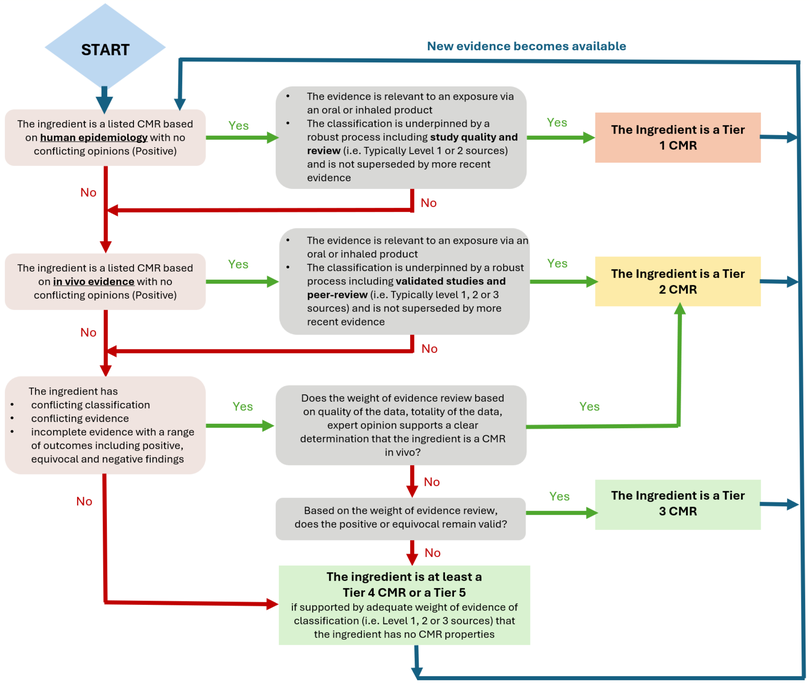


Figure 4. Decision Workflow For Tier Assignment



Tier classification must be underpinned by a weight of evidence review established based on the workflow presented in Figure 4. The weight of evidence review should first screen for any classification from authoritative sources. If conflicting or no classification has been established, the weight of evidence review proceeds by evaluating any existing experimental or in-silico data and authoritative reports. To illustrate this process, maltol [CAS# 118-71-8] genotoxicity was assessed for inhalation. In this example, no established classification has been published by the authoritative sources examined (Table 4).

Table 4. Maltol Classifications for Genotoxicity by Authoritative Bodies

Agency	Level	Primary Status / Finding	Source Conclusion	Source/Reference
IARC	1	Not examined	Not classified	IARC List of Classifications
FDA CTP	1	Based on criteria for genotoxicity in memoranda for ENDS constituents/deficiencies.	Equivocal, Potential hazard (Tier 4 classification)	FDA CTP Memo (2024)
US EPA	1	Ethyl Maltol rated "Low" health concern; non-mutagenic in Ames tests and read-across ethyl maltol. Not Classified by US EPA.	Not classified	70 FR 37686 (2005)
REACH	1	Examined in ECHA dossier	Not classified in group 1A, 1B, and 2	Table of harmonised entries in Annex VI to CLP
NTP	2	Weak positive in vitro, negative in Drosophila Germ Cell Mutagenicity	Equivocal	NTP Substance Database
JECFA	2	No safety concern at current levels as a flavouring agent.	Established as GRAS, Non-Genotoxic	JECFA FAS 56 (2006)
Cal-OEHHA	2	Not in Prop 65 list for carcinogenicity or mutagenicity.	Not Listed	OEHHA Prop 65 List
DFG	2	Not examined	Not classified	
EFSA (EU)	3	Ruled out genotoxic concern after reviewing in vivo data (Comet).	Non-genotoxic, No Concern	EFSA CEF Panel (2015)
RIFM	3	Safety assessment concluded no concern for genotoxicity.	Non-Genotoxic	RIFM Fragrance Resource
ECHA	4	Not identified as a mutagen/genotoxicant in REACH dossier.	Non-Genotoxic	ECHA Substance Info

According to the information on maltol genotoxicity collected from authoritative sources and the above workflow, Maltol has no established classification, with potentially conflicting, equivocal or incomplete evidence regarding genotoxicity. Therefore, it would potentially be assigned a Tier 3 classification pending a full weight of evidence review with the findings summarized in Table 5. The weight of evidence review indicated that equivocal or weak positive findings in vitro were not replicated in vivo but that inhalation data was lacking.

Table 5. Studies Examining Maltol Genotoxicity to Support a WoE Evaluation

Study Type	Specific Test	Model/System	Result	Reference
In Vitro	Ames Test	S. typhimurium	Negative	Bjeldanes & Chew (1979)
In Vitro	Chromosomal Aberration	Chinese Hamster Ovary (CHO)	Positive	Stich et al. (1981)
In Vitro	Micronucleus Test	Human Lymphocytes	Positive	EFSA Scientific Opinion (FGE.213Rev2) (2015)
In Vitro	BlueScreen HC Assay	Human Cell Line	Positive	RIFM (2011) & Api et al., (2025)
In Vitro	Sister Chromatid Exchange	CHO Cells	Equivocal	EFSA (2010) / JECFA
In Vivo	Pig-a Gene Mutation (oral)	Rat Erythrocytes	Negative	Misra & Carmines (2025)
In Vivo	Comet Assay (oral)	Rat Liver & Stomach	Negative	RIFM (2013) & Api et al., (2025)
In Vivo	Micronucleus Assay (oral)	Rat Bone Marrow	Negative	RIFM (2013) & Api et al., (2025)
In Vivo	UDS Assay (oral)	Rat Hepatocytes	Negative	Mirsalis (1989)

For Maltol genotoxicity, a Tier 5 determination could be supported based on negative in vivo findings but published best practice recommendations such as Dearfield et al., 2002 would advocate a Tier 4 classification. Indeed, for many ingredients, including maltol, published evidence will have examined genotoxicity in somatic but not in germ cells and data is missing in the context of inhalation. Thus, in absence of complete genotoxicity findings on both germ and inhalation, a Tier 4 classification is appropriate for Maltol genotoxicity for products such as ENDS.

CONCLUSIONS

CMR definitions and classifications differ across agencies or are not provided in many jurisdictions. This review shows that a harmonized, transparent framework is achievable. Built on high-quality evidence and weight-of-evidence principles, a consensus tiered Classification System offers a consistent, defensible basis for CMR hazard identification. Applying this approach to maltol illustrates its value: despite mixed in vitro signals, consistent negative in vivo findings and the absence of authoritative classifications and lack of germ cell data support a Tier 4 determination. This streamlined framework improves clarity, reduces inconsistency, and strengthens decision-making across global regulatory contexts to justify ingredient inclusion or exclusion.

Key References

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