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Carcinogenic, Mutagenic, or toxic for Reproduction (CMR) substances in cosmetic and personal care ingredients and products: Risk analysis and Safety assessment

Jaideep Sarkar

K R Mangalam University, India

In day to day life we as humans use lots of personal care products in form of cosmetics for beautification that indirectly leads to personality enhancement, and devices for personal hygiene like toothbrush, dental floss, sanitary napkins, adult diapers for urinary inconsistency patients or baby diapers for babies etc. All are made of many chemicals that are further made of many individual chemicals. While processing they are passed through various downstream process that involves usage of processing aids or metabolites are generated that are harmful to life. From good manufacturing practice, full care is taken to remove them all; however some entities are left over due to trace quantities that are below limit of quantification or are not detected in analytical system. One of them is CMRs. European Union (EU) classified and harmonized CMRs are those chemical ingredients that cause carcinogenicity (H340), mutagenicity (H350) and reproductive (H360) toxicity in humans when exposed for long time. These are classified under CMR substances from Annex VI of the CLP Regulation registered under REACH and/or notified under CLP with limit specified in Part 3 of Annex I of CLP Regulation (EC) No 1272/2008. They sometimes can be both genotoxic-carcinogenic or may be non-genotoxic carcinogenic or can be in either of any category 1A, 1B or 2. Since one can't fully avoid them, so various regulatory bodies have set limits and methods to derive limits for them. The general usage limit is 0.1% for carcinogen or mutagen and 0.3% for reproductive toxicant.

EU Cosmetic Ingredient Database (CosIng) has also followed the CLP list and has listed many cosmetic ingredients as CMRs as per harmonised CLP list.

Additionally, there are also flavour/fragrance ingredients that are CMRs listed by fragrance and flavour regulatory bodies (IFRA-RIFM and IOFI).

Another category CMRs are those listed under State of California's Proposition 65 (Prop65), regarded as the most conservative ones. The limits or values are called as Safe Harbour Levels that comprises of no significant risk level (NSRL) and Maximum Allowable Dose Level (MADL) values.

NSRL is for chemicals known to cause cancer or levels of exposure calculated to result in no more than one excess case of cancer in an exposed population of 100,000, expecting exposure over a 70-year lifetime (10–5 lifetime danger of malignant growth). MADL is for chemicals known to cause reproductive toxicity. At this exposure level, a chemical would exhibit no observable reproductive effect, even if 1000 times more than the MADL level is administered to a human. These two types of chemicals are preferentially totally avoided or levels much lower than NSRL and MADL is maintained. To derive those, acceptable Point of Departure values are required and mostly BMDL10 (Bench Mark Dose Level 10) for NSRL (cancer studies) and NOEL/LOEL (No Observed/Lowest Observed-Effect Level) for MADL is considered.

Additionally, if there are no available safety limits in regulatory databases, we follow ICH M7 guideline and also by EMA for deriving PDE (Permitted Daily Exposure) and OEL (Occupational Exposure Level) values, Acceptable Intake (AI) from TD50 values (daily dose rate in mg/kg body weight/day to induce tumors in 50% experimental animals) to quantify the carcinogenic potency value. PDE was derived by finding a ration between the most reliable toxicity dose level to various conditions of study (each condition is designated a numerical value: duration, quality, extrapolation, species variability, severity etc.).

The PDE is taken from the No Observed Effect Level (NO[A]EL), or the Lowest Observed Effect Level (LO[A]EL) in the most significant creature study:

PDE = NO(A)EL x Mass Adjustment

[F1 x F2 x F3 x F4 x F5]

Note: Where 'F' stands for modifying factors:

F1 = A factor to account for extrapolation between species

F2 = A factor of 10 to account for variability between individuals

F3 = A variable factor to account for toxicity studies of short-term exposure

F4 = A factor that may be applied in cases of severe toxicity, e.g., non-genotoxic, carcinogenicity, neurotoxicity

or teratogenicity.

F5 = A variable factor that may be applied if the NO[A]EL was not established {ex.: 10 for a Lowest-Observed-

Adverse-Effect Level (LOAEL)}

There were stances when no safety comparator or Point of Departure (POD) value could be derived; especially in case of naturals or herbal or polyherbal compositions extracts or polymers or any chemical who's chemical identity could not be established based, in-silico methods like Q(SAR) were used to derive clinical safety values.

Various software's are available for in-silico prediction like TTC, OECD QSAR Toolbox, Danish QSAR, DEREK NEXUS etc. They on basis of SMILES formula, directly give a clinical value and categorise them as genotoxic or non-genotoxic. However, due to limited availability, TTC by Toxtree, EPA Comptox and OECD QSAR tool box was used. Softwares scrutinised the chemicals and classified them is various Cramer Classes and a TTC value was assigned accordingly: Class I (30 µg/kg-bw/day) or II (9 µg/kg-bw/day) or III (1.5 µg/kg-bw/day), respectively; with Class III to be most conservative and toxic.

However, in many cases; cosmetics or personal care products were not meant to be used lifetime. So conservative approach was not used and PDE values for limited exposure time period was derived based on ICH

M7 guidelines. This approach is basically for new drug substances and new drug products. It is based on TTC values of acceptable intake (AI). AI of 1.5 µg/person/day for a mutagenic impurity is considered to pose negligible risk (theoretical excess cancer risk of 10 years). However, if there is considerable data gaps, this approach can be used for impurities that are mutagenic with no carcinogenic data and has to be used for long term treatment (>10 years).

Finally, the % or concentration of CMR in any chemical claimed by the manufacture was evaluated and if it's found less than the regulatory/derived limits, we concluded them to be safe for human use. In this was we evaluated the safety limits of CMRs and risk assessment was completed. Holistically, safety assessment of cosmetics and personal care products was completed..