Evaluating Quaternary Ammonium Compounds (QACs)

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Introduction

- The Quat Residue Group (QRG) and ADBAC & DDAC Issues Steering Committees are consortia that jointly address toxicology and regulatory requirements for quaternary ammonium compounds (QACs) in the US and Europe
- Member companies make sanitizing and disinfecting products and three member companies also manufacture the active ingredients

Evaluating QACs

- QACs have been extensively evaluated for safety
  - Robust studies confirm the large human safety factors associated with uses
- Uses are supported by large consistent data sets in multiple species
- GLP-compliant studies show irritant potential but *not* systemic effects
- QACs are regularly evaluated and are approved for a broad range of uses
- QACs have a long record of safety and importance in protecting human health

QACs as Ingredients in Sanitizing and Disinfecting Products

- Regulated in US by EPA (FIFRA)
- Regulated in Europe by ECHA (BPR)
- Regulated in California by DPR (Cal EPA)
- Registrations as active ingredients are based on extensive human and ecological safety testing as well as human exposure monitoring and assessment
- QACs are present at low concentrations (0.1% is typical) as ingredients in sanitizing and disinfecting formulations that also require registration
- QACs have a long history of efficacy and safety in residential, commercial, and healthcare applications when used according to directions

QACs Toxicology Dataset Overview

- Environmental Fate and Effects
- Mammalian ADME (absorption, distribution, metabolism, excretion)
- Acute Toxicity tests for oral, dermal, and inhalation exposures
- Skin and Eye Irritation (irritant or non-irritant at typical use concentrations)
- Skin Sensitization (negative)
- Genotoxicity (negative)
- Repeat Dose Toxicity (multiple exposure routes, multiple species, clear effect and no effect doses identified, point of contact effects only)
- Carcinogenicity (negative in multiple species)
- Developmental and Reproductive Toxicity (negative in multiple species and in multigenerational studies)

Toxicology Summary

- QACs are readily biodegradable
  - Strongly adsorptive and rapidly partition to soil and sediment making them immobile and unlikely to leach or accumulate in surface or ground water
- QACs do not produce systemic toxicity
  - QACs are poorly absorbed (< 10% orally, < 10% dermally)
  - QACs do not bioaccumulate
  - No adverse effects in target tissues distant from point of contact
- QACs are point-of-contact irritants
  - Irritant effects are time- and concentration-dependent
  - No effect concentrations in animal tests are far greater than amounts found in dilute, end use products, sometimes by a factor of 100 or more
- Results are markedly consistent across many species

Developmental and Reproductive Toxicology Study Findings

- As required by GLPs, careful attention paid to dose range-finding and definitive studies
  - Study design must meet criteria to allow for use in human health risk assessment
- Critical study features
  - Guideline-recommended species and strains
  - Adequate sample sizes
  - Full characterization of test substance
  - Confirmation of accuracy of doses administered
  - Documentation of overt toxicity, evidenced by changes in body weight, food consumption, clinical signs, etc.
- Result: Rigorous experimental design and execution produced valid, reproducible data supporting accurate interpretations and conclusions that ADBAC and DDAC do not produce reproductive toxicity

Overview of Key Developmental and Reproductive Toxicology Studies on ADBAC and DDAC

- Developmental toxicity
  - Conducted in rats and rabbits, as per regulatory guidelines
  - Oral route of administration is required by guidelines
    - This is a negligible, unlikely route of exposure in humans
  - No evidence of teratogenic effects
  - Clear effect and no effect doses were identified for other toxicity endpoints
  - Effects on pregnant female animals are seen only at highest doses tested
    - These doses are far in excess of human exposures
- Reproductive toxicity
  - Guideline-compliant studies (2) in rats, the recommended species in regulatory guidelines
  - No effects were observed for any reproductive measures or parameters
  - Clear effect (minor, dose-related body weight changes) and no effect doses were identified in parental and offspring generations

Regulatory Review of Developmental and Reproductive Toxicology Studies with QACs

- In dozens of studies in mice, rats, rabbits, and dogs, there has been no evidence of changes to endocrine-responsive tissues following short-term or long-term exposure to QACs by oral, dermal, or inhalation routes
  - No reproductive effects were seen in properly conducted guideline studies
- US EPA and ECHA independently concluded that developmental and reproductive studies are complete and meet all requirements for data quality and study reliability
  - ADBAC and DDAC have never been classified as developmental or reproductive toxicants
- Wide safety margins exist, based on no effect doses in animal studies that greatly exceed estimates of human exposure
  - Example: ADBAC (rat) NOAEL = 100 mg/kg; Human exposure = 0.0159 mg/kg
  - Margin of Exposure (safety factor) = 6,289; EPA Target = 100

Exposure Potential to QACs

- Potential human exposures to QACs are well documented and known to be very low
- Food contact uses are approved for QACs in California, US, Europe, and globally
- QACs are non-volatile; inhalation exposures are negligible
- QACs data sets for acute, developmental, reproductive, and chronic toxicity/carcinogenicity endpoints demonstrate the safety of these active ingredients

Conclusions

- QACs have been extensively evaluated for acute, developmental, reproductive, and chronic toxicity/carcinogenicity endpoints
- GLP-compliant studies show there is no evidence of cellular changes in tissues distant from the point of contact
    - These include high-dose, short term studies as well as subacute, subchronic, and long-term toxicity studies in mice, rats, rabbits, and dogs, from all routes of exposure – inhalation, oral, and dermal
- Broad uses are supported by large consistent data sets
- Adverse effects in robust guideline studies (point of contact irritation, reduced body weight gain in feeding studies, etc.) occur at doses that greatly exceed human exposure to QACs
- Approvals demonstrate confidence in the strength of the QACs data sets
- QACs are approved and widely used because of their safety profiles and importance in protecting human health in the face of existing and emerging pathogens