Potential Priority Chemicals:
Quaternary Ammonium Compounds

Materials for March 8, 2021 Meeting of the Scientific Guidance Panel
for Biomonitoring California[1]

At the March 2020 meeting of the Scientific Guidance Panel (SGP), the Panel recommended including the class "quaternary ammonium compounds (QACs)" as designated chemicals for Biomonitoring California. The class of QACs is diverse and includes hundreds of chemicals and chemical mixtures. QAC structures generally include NR_4^+, where R is often an alkyl or benzyl group.

The class of QACs is now under consideration by the SGP as potential priority chemicals. The criteria for recommending priority chemicals are specified in the Program's enabling legislation (SB 1379[2]) and are listed below.

- The degree of potential exposure to the public or specific subgroups, including, but not limited to, occupational.
- The likelihood of a chemical being a carcinogen or toxicant based on peer-reviewed health data, the chemical structure, or the toxicology of chemically related compounds.
- The limits of laboratory detection for the chemical, including the ability to detect the chemical at low enough levels that could be expected in the general population.
- Other criteria that the panel may agree to.

For the SGP's prior deliberations on QACs, OEHHA developed the following documents:

- Preliminary Screening of Quaternary Ammonium Compounds for Future Consideration as Potential Designated Chemicals (OEHHA, 2019)
- Potential Designated Chemicals: Quaternary Ammonium Compounds (OEHHA, 2020)

These documents include information relevant to the priority chemical criteria. Table 1, starting on the next page, briefly describes selected recent references on QACs that were not included in OEHHA (2019; 2020). After Table 1, we provide some information related to limits of laboratory detection.

QACs have a wide range of uses, including as antimicrobials and disinfectants in consumer products. Use of these products has increased during the COVID-19 pandemic. A recommendation by the SGP to add this class to the priority list would highlight the importance of measuring and tracking Californians' exposures to known and emerging QACs.

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[1] California Environmental Contaminant Biomonitoring Program, codified at Health and Safety Code section 105440 et seq.

[2] SB 1379, Perata and Ortiz, Chapter 599, Statutes of 2006, available at: https://biomonitoring.ca.gov/sites/default/files/downloads/sb_1379_bill_20060929.pdf.

Table 1. Selected recent references on QACs[1] (listed in alphabetical order within each category)

Potential human exposure	**Reference**
• Information on ~800 QACs used in Canadian commerce in 2017, including reported substances, commercial applications, and intended use, was made publicly available.	Government of Canada (2020)
• An exposure assessment of disinfecting chemicals, including 14 QACs, using an indoor fate and chemical exposure model estimated whole-body uptake and blood concentrations for three age groups.	Li et al. (2020)
• ~46% of products on List N: Disinfectants for Coronavirus (COVID-19) include QAC active ingredients.	US EPA (2021a)
• Indoor dust samples from Indiana homes were tested for 19 QACs. Summed QAC concentrations were significantly higher in samples collected after the emergence of the COVID-19 pandemic compared to pre-pandemic dust samples, and in homes that were disinfected more frequently compared to less frequent disinfection. QAC profiles in dust were similar to those in three disinfecting products used in many of the homes.	Zheng et al. (2020)
Toxicity	**Reference**
• Some immune effects were observed in lupus-prone mice exposed to ambient levels of a QAC-containing disinfectant[2] via either cage wash or use in the animal facility.	Abdelhamid et al. (2020)
• Immunological responses were studied for selected antimicrobials, including two QACs. Altered expression of immune response genes was observed in various tissues collected from mice dermally exposed to either benzalkonium chloride or didecyldimethylammonium chloride (DDAC).	Anderson et al. (2020)
• Nasal cavity and lung irritation were observed in rats exposed to aerosolized benzalkonium chloride over a 14 day period. Based on observed histopathological changes, the authors concluded that the irritation was caused by reversible oxidative damage.	Choi et al. (2020)
• QACs were included in a literature review of respiratory effects from exposure to chemicals in cleaning and disinfection products. The authors cited previously published studies that identified QACs as both sensitizers and irritants in causing asthma; specific inhalation challenge studies in asthmatic workers that indicated that QAC-containing products may cause sensitizer-induced asthma; and animal and human inhalation exposure studies of benzalkonium chloride that reported inflammation and bronchoconstriction. However, the authors noted that the mechanisms for QAC-related asthma are not clear and described significant limitations in studies of respiratory effects, including the presence of co-occurring chemicals of concern and the unreliability of self-reported exposure measures in epidemiological studies. They called for an integrative assessment of cleaning chemicals that would address a range of factors, such as indoor microclimate and individual susceptibility. As a research need, they stated that, “Better characterization of personal exposure should be obtained from controlled experimental exposure studies combined with objective health measures of asthma versus healthy subjects.”	Clausen et al. (2020a)

Table 1 (cont.)

Toxicity (cont.)	Reference
• Kim et al. conducted *in vivo* and *in vitro* experiments to assess the pulmonary toxicity of cetylpyridinium chloride (CPC). Rats were exposed via intratracheal instillation or in an inhalation chamber (acute: 4 hours; or subacute: 6 h/day, 5 days/week for 28 days). As one finding in each of these three experiments, the authors reported increased levels of polymorphonuclear leukocytes, an indicator of pulmonary inflammation, in rat bronchoalveolar lavage fluid and noted that "the strong inflammatory effects of CPC persisted in the rat lungs for at least 7 days post exposure."	Kim et al. (2021)
• A human health hazard assessment of alkyl (C12, C14, C16) dimethyl benzyl ammonium chloride (C12-C16 ADBAC) and didecyl dimethyl ammonium chloride (DDAC) relied on "available peer-reviewed literature and unpublished data submitted to and summarized by regulatory agencies" (i.e., US Environmental Protection Agency [US EPA] and European Chemicals Agency [ECHA]) to support antimicrobial product registration. The authors concluded that "the main concern associated with exposure to DDAC and C12-C16 ADBAC is local effects through irritation."	Luz et al. (2020)
Other recent publications	**Reference**
• An assessment of the ecological hazards and environmental fate of disinfectant QACs (alkyl dimethyl benzyl ammonium chloride compounds and dialkyl dimethyl ammonium chloride compounds) used peer-reviewed literature and unpublished studies submitted to and reviewed by regulatory agencies (i.e., US EPA and ECHA) to support antimicrobial product registration.	DeLeo et al. (2020)
• A framework for deriving Occupational Exposure Limits (OELs) for antimicrobial agents was illustrated using a QAC-containing disinfectant product as a case study. The selected OEL of 0.1 mg/m^3 was based on a derived no effect level (DNEL) for "quaternary ammonium compounds, benzyl C12-C16 (even numbered)-alkyldimethyl chlorides" (ECHA, 2021). This OEL was considered by the authors "to be protective of all potential identified adverse health outcomes," including irritant toxicity and developmental and reproductive toxicity.	Dotson et al. (2020)
• Estimated photolysis half-lives of various QACs in surface and river waters were ~12-94 days.	Hora and Arnold (2020)
• A San Francisco Estuary Institute (SFEI) report briefly summarized results of analyses conducted by Dr. Bill Arnold at the University of Minnesota for 14 QACs in samples of San Francisco Bay sediment. Seven analytes were detected at two or more sites. The benzylalkyldimethyl ammonium compound-C18 was the most widely detected, and the dialkyldimethyl ammonium compound-C18 was detected at the highest concentrations.	SFEI (2020)
• US EPA's Preliminary Work Plan for cetylpyridinium chloride as a materials preservative (e.g., in construction materials and textiles/fabrics/fibers) includes a summary of data that would be needed to support the registration of these uses.	US EPA (2020)

[1]Nomenclature for QACs in Table 1 matches that used by reference author(s).
[2]From Abdelhamid et al. (2020), the QAC-based disinfectants "CP-64 or Labsan 256" were used.

Limits of laboratory detection

Biomonitoring California recently conducted a pilot study in collaboration with Dr. Libin Xu at the University of Washington. Urine samples were tested for six carboxylic acid metabolites of benzylalkyldimethyl ammonium compounds. The method detection limits for the metabolites ranged from ~20-30 ng/L.

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Office of Environmental Health Hazard Assessment (OEHHA) documents on QACs

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