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Is it time to re-evaluate exposure risks to quaternary ammonium compounds as disinfectants?

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The use of disinfectants is a hallmark of infection prevention and control (IPAC) in general. Over the decades, various chemicals have been manufactured and sold for this purpose. Today over 4 billion dollars of disinfectants are purchased annually in the United States alone (Grand View Research, 2021). This amount has nearly doubled in recent years mainly due to the COVID-19 pandemic, with quaternary ammonium compounds (QACs) representing nearly one-third of the entire market. The rapid increase in the marketing and subsequent uptake of QACs is due in part to their rapid acceptance by government regulators as being active against SARS-CoV-2 (Diderich and Poret, 2020; US EPA, 2020).

Apart from disinfectants, QACs also provide antimicrobial activity to a variety of personal care products including shampoos, toothpastes and nasal sprays as well as other health-based products such as eye drops, and lotions. The ubiquity of QACs continues to grow as they are also used as antifouling agents for a variety of medical devices including bone and dental restorative implants (Featherstone, 2022; Gao et al., 2023).

There is little doubt of the prominence of QACs and from an IPAC perspective, this may seem beneficial. However, there are emerging safety concerns that need to be addressed. This stems from the fact that QACs naturally demonstrate a curariform-like activity (Ing et al., 1931; Warren et al., 1942) with a potential for human toxicity (Arro and Salenstedt, 1973). While there have been no dose-dependent toxicological studies in humans, there have been reports of deaths associated with acute ingestion of significant amounts of benzalkonium chloride (Adelson and Sunshine, 1952; Spiller, 2016; Tambuzzi et al., 2022). Studies in mice and rabbits suggest an oral dose of 100–400 mg/kg would be considered life threatening (Arro and Salenstedt, 1973; Lee and Park, 2019; Warren et al., 1942). Non-lethal injuries have been seen with acute exposure including esophagitis (Civan et al., 2016), respiratory dysfunction (Okan et al., 2007), and pneumonitis (Nițescu et al., 2024) particularly in children. In France, evidence suggests the number of these cases has risen over the last four years due to increased use of QACs due to COVID-19 pandemic (Le Roux et al., 2021). Yet, as De Leo et al. have demonstrated (DeLeo et al., 2021), the potential for toxic effects lie primarily with ingestion as overuse of an antiseptic handwash containing benzalkonium chloride resulted in no systemic exposure or effects.

There is little doubt of the dearth of information that exists on toxicity associated with chronic low-level exposure. Instead, limits are based on antiquated evidence. The European Food Safety Authority has determined that a health standard of 100ppb residual QACs would be implemented for any dietary food (European Food Safety Authority, 2014). In the United States, the EPA has regulated not the residual concentration but rather the in-use concentration of QACs to 200 ppm in order to reduce the potential for residual contamination (Federal Register, 2021) . With this limit in mind, several recent studies in both humans and animal models have examined the effects of QACs at these levels to better understand the potential impact on human health. The results have provided enough evidence to consider re-evaluating exposure risks.

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QACs in blood

Hrubec et al. (Hrubec et al., 2021) examined blood samples from 43 participants and found part per billion levels of persisting QACs. This was then associated with parameters such as cytokine production, sterol breakdown, and mitochondrial function. In comparison to controls, the authors calculated a 0.5 and 0.9 correlation between the concentration of QACs in the blood and the effect on the tested parameters. Specifically, the presence of QACs increased cytokine levels associated with inflammation, increased the levels of cholesterol intermediates and decreased mitochondrial function. These levels were significantly lower than the exposure limits stated above but due to chronic exposure, they increased within the body leading to the observed outcomes.

QACs and cellular stress

When QACs meet eukaryotic cells, a stress response is initiated (Herron et al., 2021, 2019; Jeon et al., 2019; Rogov et al., 2020). Although the adverse events mentioned above were associated with internal exposure, there is also the potential for inflammatory sequelae with general exposure. Indeed, even as DeLeo et al. (DeLeo et al., 2021) did not find systemic effects associated with hand antisepsis, others have shown acute sensitivities (Dear et al., 2021; Migueres et al., 2021; Peyneau et al., 2022) such as urticaria, contact dermatitis, and asthma associated with long-term exposure. The development of cellular stress during exposure is the unifying factor for these and many other adverse events. To minimize the potential for stress, reduction of use would be the best recommendation.

QACs and immunity

As observed by Hrubec et al. (Hrubec et al., 2021), there is a link between QAC concentration in the blood and altered cytokine production leading to an inflammatory profile. Abdelhamid et al. (Abdelhamid et al., 2020) explored this further in a mouse model examining the impact on immunological function. Using natural exposure to residues of QACs, the authors determined that there was indeed a shift in cytokines towards inflammation and oxidative stress. However, there was also an alteration in the development of the immune response. Specifically, the normal route of identifying and eliminating foreign agents, including tumours, was hindered. This led to the loss of cellular immunity through the depletion of T-cells. What makes this study even more concerning is that the mice were exposed passively much in the same way humans are exposed after using QAC-based disinfectants in healthcare facilities and in the home.

QACs and neurological health

As Hrubec et al. (Hrubec et al., 2021) discovered, cholesterol production was significantly affected by the presence of QACs in the blood. While this may appear at first to be a beneficial effect, there may be a drawback at the neurological level. Myelin, which is a fatty substance that aids in proper neurotransmission in the brain, requires cholesterol and a lack of production may lead to reduced myelin formation. However, as Cohn et al. (Cohn et al., 2024) have demonstrated, the presence of QACs may prevent the formation of myelin not through a reduction in cholesterol but through a reduction in the cells that make myelin, oligodendrocytes. Using a mouse model to examine the effects of compounds such as cetylpyridinium chloride (CPC), which is ubiquitous in personal hygiene products such as oral rinses and fresheners, they found that developing oligodendrocytes in the brain were sensitive to exposure and instigated a stress response that led to cell death. The levels tested were in the sub 100ppb concentration range, which is the predicted range of these compounds in the human bloodstream (Li et al., 2020; Zheng et al., 2021). While the likelihood of an acute exposure to this level of QACs in the brain is low, the potential for accumulation as seen by Hrubec et al. (Hrubec et al., 2021) suggest long-term exposure may lead to these toxic levels over time.

QACs and reproductive health

Another outcome from Hrubec et al. (Hrubec et al., 2021) is the concentration-dependent disruption of mitochondrial function. Mitochondria are essential for energy production although dysfunction can normally be mitigated by other cellular processes. The only exception is oocytes, which require proper mitochondrial function for optimal embryonic development. Liu et al. (Liu et al., 2023) utilized this dependence along with the evidence that QACs can pass through the placental barrier to determine the extent of mitochondrial dysfunction in developing mouse oocytes associated with exposure to CPC. Not only was there a reduction in the development of oocytes but also a reduction in the number of oocytes in the mice. The effect was mediated through the development of oxidative stress. Although the concentrations used for exposure were significantly higher than normal residual amounts, the outcomes demonstrate the potential deleterious effects of mitochondrial dysfunction associated with chronic QAC exposure.

Conclusion

There is little doubt QACs are effective antimicrobials against bacteria and enveloped viruses. However, with the rise of COVID-19 and the unprecedented ramp up in use of QACs, the potential for negative impacts to human health are growing. Although a reassessment of the potential for toxicological outcomes and requirements for reduced limits for residual exposure might not appear to be useful, such a task was performed in the 1980s leading to a marked reduction in use (Pati and Arnold, 2020). It would be prudent to begin examining the effects of QAC exposure in various areas where it is being used extensively such as the households, schools, hospitals, and restaurants. However, what might be a better choice for infection preventionists to examine other safer formulations that may offer equal, if not better, disinfecting efficacy. This potential changing of the guard may seem to be unnecessary to some and possibly even extreme to its proponents, but the process is not novel. Several types of disinfectants such as aldehydes and chlorine-based disinfectants have experienced a reduction in use in IPAC due to safer and/or more effective options. The time may be right to once again look at changing our ways to preserve our future health.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Faraz Alderson reports a relationship with Virox Technologies Inc that includes: employment. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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