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Survey of Neurotoxicants Released from Medical Devices

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Background and Purpose: Medical devices are made of a diverse range of materials (*i.e.*, plastics, metals, and polymers), which may release various compounds into the patient's body during clinical use that may act as neurotoxicants, adversely affecting the central and peripheral nervous systems and sensory organs. Neurotoxic effects range from reversible symptoms, like narcosis, nausea, and dizziness, to irreversible outcomes, such as neurodegenerative disorders. ISO/FDIS 10993-1:2025 emphasizes medical devices contacting the central or peripheral nervous system or cerebrospinal fluid must undergo neurotoxicity evaluation, including consideration of local (*e.g.*, effects near the device) and systemic (*e.g.*, neurological effects throughout the body) neurotoxicity. Currently, no comprehensive reference list exists for neurotoxicants associated with medical device extractables. By comparing identified neurotoxicants against robust, published datasets of medical device extractables, we aim to create and classify a consolidated reference list of neurotoxic substances identified from medical device materials.

Methods: Craenen *et al*. (2025) recently published a reference list of industrial chemicals classified as neurotoxic in accordance with classifications listed in Classification, Labelling, and Packaging (CLP) for hazard classification. We screened this reference list of neurotoxic substances against datasets of chemicals established to be released from medical devices recently published by Builee *et al*. (2025), and Borton *et al*. (2025). Next, the identified chemicals were categorized according to Specific Target Organ Toxicity Single Exposure (STOT SE) and STOT Repeated Exposure (STOT RE), as defined in CLP Annex V and the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). GHS category 1 chemicals produce and/or presumed to have significant toxicity in humans based on evidence from studies in experimental animals following a single and/or repeated exposure. Similarly, GHS category 2 chemicals have the potential to produce significant toxicity in humans, solely based on evidence from studies in experimental animals following a single and/or repeated exposure. Finally, GHS category 3 chemicals may produce transient target organ effects only after a single exposure.

Results: From 113 neurotoxicants identified by Craenen *et al.* (2025), 60 unique chemicals were found in at least one of the two medical device extractables datasets. A majority of the identified compounds (53 chemicals) were classified as STOT SE3, causing narcotic effects and respiratory tract irritation, and have no fixed pre-defined limits for the exposure guidance values (under GHS). Two compounds, resorcinol and cyfluthrin, were classified as STOT SE1 and are associated with oral (lowest observed adverse effect level [LOAEL] ≤ 300 mg/kg-bw) or gas inhalation (lowest observed adverse effect concentration [LOAEC] ≤ 2,500 parts per million per volume [ppmV]/4 hours) exposure ranges in rats. In addition, three neurotoxicants (ethylene oxide, bifenthrin, and indoxacarb) were classified as STOT RE1, indicating LOAELs/LOAECs of ≤ 10 mg/kg-bw/day for oral exposure and ≤ 50 ppmV/6 hours/day for gas inhalation exposure in rats. Two neurotoxicants (cypermethrin and mesotrione) were identified as a STOT RE2 classification, with LOAEL/LOAEC ranges of 10 to ≤ 100 mg/kg-bw/day for oral exposure and > 50 to ≤ 250 ppmV/6 hours/day for gas inhalation exposure in rats.

Conclusions: Our findings establish a consolidated reference list of neurotoxicants associated with medical device extractables by screening harmonized neurotoxicity classifications against two robust

extractables datasets. Among the 60 unique chemicals identified in medical device materials, the majority were classified as STOT SE3, indicating transient neurological effects. A smaller subset exhibited higher toxicity classifications (STOT SE1, STOT RE1, and STOT RE2) following single or repeated exposure. Further delineation of the type and source of these chemicals will be presented in future research. This reference list helps with proactive screening of neurotoxic compounds and supporting manufacturers in meeting evolving standards, particularly for devices that contact nervous system tissues or cerebrospinal fluid, as required by ISO FDIS 10993-1:2025.