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Endocrine Disruptors in Medical Devices: An Integrated Approach for Compliance with Regulatory Requirements

Abstract

Endocrine Disrupting Chemicals (EDCs) in medical devices (MDs), according to European Medical Device Regulation (EU MDR) 2017/745[1] establishes some general requirements under Annex I, Chapter II, Section 10.4., CMR (Carcinogens, Mutagens and Reproductive Toxicants) and Annex II, Technical Documentation, but they are limited in scope and detail regarding toxicological evaluations, leaving to individual stake holders to prepare guidelines for use and safety. Presently, without specific legislation to effectively respond to toxicological concerns, manufacturers working with EDCs are also guided by ECHA/REACH[2] and Biocidal Products Regulations[3]. Most recently, health risk assessments of potential EDCs have called for the need of systematic and universally accepted evaluative approaches, particularly in the expanding area of environmental health science. To this end, the World Health Organization (WHO) has reported on the identification of risks of endocrine disrupting chemicals with the purpose of establishing methodologies for assessing the risk of endocrine disrupting chemicals to human health, and for incorporating exposure to EDC health surveillance into the design and performance of epidemiological studies fundamental to building the capacity necessary to address problems related to EDCs at the national and international levels[4].

It is important to highlight that the aim of the EU MDR is to ensure the functioning of the European and by extension, US market with regard to MDs, concomitant with the reduction of the risks posed by substances/particles that may be released from them. Moreover, MDs should not contain substances of concern (like carcinogenic, mutagenic, toxic for reproduction substances and/or EDCs), and manufacturers and suppliers are strongly encouraged toward the use of alternate materials. As a general guideline, their presence, where necessary should be no greater than a concentration above a 0.1% w/w threshold.

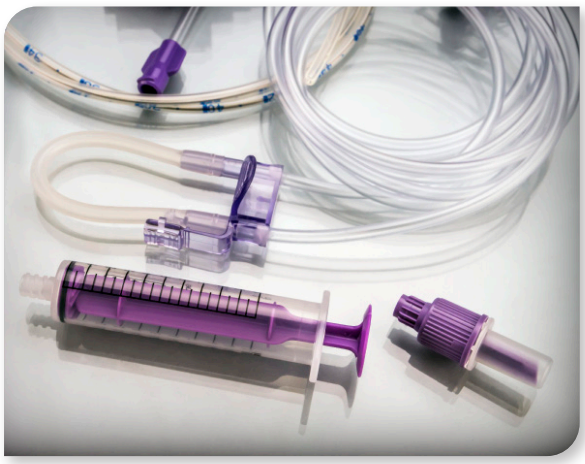
The goal of the present paper is to propose a systematic, standard workflow for the safety assessment of endocrine disruptors through the understanding of what EDCs are, where they are found and how to mitigate their exposure via the performance of the biological evaluation of MDs, followed by the evaluation of the known EDCs as established by ECHA for the verification of the test method proposed, all in the context of a pragmatic, operational workflow.

Endocrine Disruptor Chemical Identification

Endocrine disruptor chemicals (EDCs) are synthetic or natural chemicals that may mimic or interfere with endocrine (or hormonal) systems at certain doses. For a substance to be considered an EDC it must show an adverse effect in both humans and wildlife. Most EDCs identified to date interact with hormone receptors as agonists or antagonists, but others act via altering hormone "production, release, transport, metabolism, binding, action, or elimination"[5]. In 2015 the Endocrine Society released a statement on endocrine-disrupting chemicals specifically listing obesity, diabetes, female reproduction, male reproduction, hormone-sensitive cancers in females, prostate cancer in males, thyroid, neurodevelopment and neuroendocrine systems as being affected biological aspects of being exposed to EDCs[6]. Found in many household and industrial products, endocrine disruptors are substances that "interfere with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for development, behavior, fertility, and maintenance of homeostasis (normal cell metabolism)"[7]. The term endocrine disruptor was coined

at the Wingspread Conference Center in Wisconsin, in 1991 from an earlier awareness brought by Rachel Carson's 1962 book "Silent Spring". One of the early papers on the phenomenon was by Colborn et al. in 1993 who noted from this time that environmental chemicals disrupt the development of the endocrine system and that effects of exposure during development are often permanent[8]. Considered endocrine disrupting-related chemicals include DDT, polychlorinated biphenyls (PCB's), bisphenol A (BPA) and S (BPS), polybrominated diphenyl ethers (PBDE's), perfluoroalkyl and polyfluoroalkyl substances (PFAS), dioxins, perchlorates and organophosphates, phytoestrogens, triclosans and phthalates, among others. For each EDC the dose and the route of exposure should also be considered. Food is a major mechanism by which people are exposed to pollutants. Diet is thought to account for up to 90% of a person's PCB and DDT body burden. Since these compounds are fat soluble, it is likely they are accumulating from the environment in the fatty tissue of animals we eat[9]. After the oral route, the dermal and the inhalation route of exposure are usually the most common, but the possible in utero exposure and the exposure of the offspring during lactation is also critical during the reproductive lifetime of the individual[10]. The embryo and the fetus, particularly, without a proper developed blood brain barrier and with rudimentary DNA repair mechanisms, are considered to be more susceptible to exposure compared with adults.

Endocrine Disruptors in Medical Devices & Biological Evaluation



A Medical Device (MD) is defined as any instrument, apparatus or implant, designed to be used alone or in combination for medical purposes apart from any pharmacological, immunological or metabolic mode of action.

The FDA defines a medical device as[11]:

- "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them;
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or;
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

The biological evaluation of MDs follows the standard ISO 10993 - "Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process"[12] and FDA (2016) "Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"[13] guidance. Critically, it is important to note that internationally, the first step of this process is the chemical characterization of MDs. That is the separation, identification, and quantification of each component of a complex mixture of compounds following the standard ISO 10993-18 (2020) "Biological evaluation of medical devices — Part 18: Chemical characterization of medical device materials within a risk management process"[14]. Chemical analysis of the given medical device is the chief determinant of the presence of any extractables and leachables, specifically that of endocrine disruptors, that may be released under exaggerated conditions and/or in standard clinical use.

During this process, extracts of the medical device are generated from incubation at specified time points

in model solvents:

- Polar solvents: water, physiological 0.9% saline,
- Semi-polar solvents: isopropyl alcohol, ethyl alcohol, alcohol/water
- Non-polar solvents: hexane.

Samples of the extracted solutions are typically analyzed via spectrometric techniques, most often through:

- HPLC-UV/MS: Non-volatile organic compounds;
- GC/MS: Semi-volatile organic compounds;
- ICP/MS-OES: Inorganic/elemental compounds.

Endocrine Disruptor Chemical Screening & Evaluation

The objective of risk assessment of chemicals is to evaluate the available scientific data in order to provide a sound scientific basis for decision makers to act (if needed) to reduce probable risks to human health and/or the environment. In this context, toxicological data is reviewed to identify any and all possible adverse effects to determine a tolerable/safe dose. Generally, the risk assessment process consists of three main parts: hazard assessment (including hazard identification and hazard characterization), exposure assessment, and risk characterization[15].

In hazard assessment, including hazard identification, a review of ED toxicological information through the available literature and databases is an initial and prospectively rich source of information. These sources may include databases PubMed, ECHA, ASTDR, ToxPlanet, among others. Under European Chemicals Agency (ECHA) and Registration, Evaluation, Authorization and Restriction of Chemicals (REACH), endocrine disruptors may be identified as substances of very high concern (SVHCs), where there is scientific evidence of probable serious effects to human health or the environment. ECHA has compiled such an ED list at: https://echa.europa.eu/it/ed-assessment, which is periodically updated (presently January, 2020) as needed. ECHA's endocrine disruptor (ED) assessment list includes the substances undergoing an ED assessment under REACH or the Biocidal Products Regulation that have been brought for discussion to ECHA's ED Expert Group.

Often, in an attempt to identify sources of EDs, their use and presence vis-a-vis manufacturing and composition for plastic products, including those in medical devices, is realized.

The ECHA listing has the advantages of subdividing the composition of plastics into their respective individual and potentially hazardous components for thorough chemical characterization. For example, in the case of EDs in plastics the compilation can subdivide all the ED substances identified into 4 different classes of which among them 4 different phthalates (DEHP, DBP, BBP and DiBP) and 2 different phenolic compounds (Bisphenol A and 4-t-octyl phenol) are considered by ECHA as EDCs as released by plastic materials. These 6 compounds may then comprise the EDCs list which may subsequently be used to choose the most reliable in silico method (Danish QSAR Toolbox and VEGA HUB, for example) to perform the toxicological safety prediction and verify the already known and accepted toxicological account for that chemical.

General Workflow Proposed

With the purpose of defining a standard safety evaluation practice for ED chemicals as they are identified upon analytic determination, a systematic workflow is proposed.

Integral to the safety evaluation of EDCs is the appropriate chemical characterization of the given medical device per ISO 10993-12 (2012), -18 (2020)[14], [16].

Once the pertinent extractables and leachables are identified through the chemical analysis, this quantitative information is used to establish the proper TTC value for genotoxic impurities, according to the Class categorization of the

MD itself[17], [18] under worst-case scenario of use.

Evaluation of the genotoxicity (mutagenicity/clastogenicity), both in vitro and in vivo end-points for exposure assessment can be divided into three possible toxicological scenarios followed by determination of the ED risk potential (assessment):

1. Known Compounds with Sufficient Toxicological Data: for known compounds identified during the chemical characterization of MDs, toxicological evaluation can be performed by calculating the safe tolerable intake in order to derive a final proposed tolerable exposure, according to the standard ISO_WD 10993-17, derived from ISO 10993-17 (2002)[17], now under revision.

2. Known Compounds without Sufficient Toxicological Data: without sufficient toxicological data for the known compounds identified during the chemical characterization of the given MD, it is possible to perform a read-across from structurally similar chemical compounds and their structural alerts (toxicophores), traditionally used to signal toxicity.

To conclude, for any of the known organic compounds identified during the chemical characterization of the given MD that are also present on the list of EDCs as previously determined, a toxicological evaluation is performed using the tolerable intake and the final proposed tolerable exposure (according to the standard ISO_WDI 10993-17, in process) for the given population of exposure.

3. Known compounds with No Toxicological Data: if there are no toxicological data for the known compounds identified during the chemical characterization of the given MD, it is advised to perform an in silico prediction using acceptable and validated methods from computational resources (i.e., methods, algorithms, software, data, etc.) to organize, analyze, model, simulate, visualize, or predict toxicity of chemicals.

Subsequent to the in silico prediction under these latter circumstances, it is possible to calculate the tolerable intake in order to derive a final proposed tolerable exposure, according to the standard ISO_WDI 10993-17, in process.

Once the evaluation of the genotoxicity end-point is concluded, the endocrine disrupting potential of the given MD can be determined (risk characterization). Associated with genetic hazard assessment, toxicological risk is often based on experimental, preferably long-term, animal data from studies performed in accordance with reliable standardized test guidelines (OECD) which examine validated endpoints of reproducibility (No Adverse Effect Level) as the point of departure for a safe human tolerable dose; if human data is available it is used as supportive evidence. “The exposure assessment aims to identify all sources of exposure to a compound and estimate exposure levels in the population of interest, e.g. the general population, certain workers, or a certain age group”[14].

In addition to possible systemic long-term effects, consideration of local, short-term end-points such as skin irritation/corrosion/sensitization lend importance in MD toxicological evaluation for EDs since:

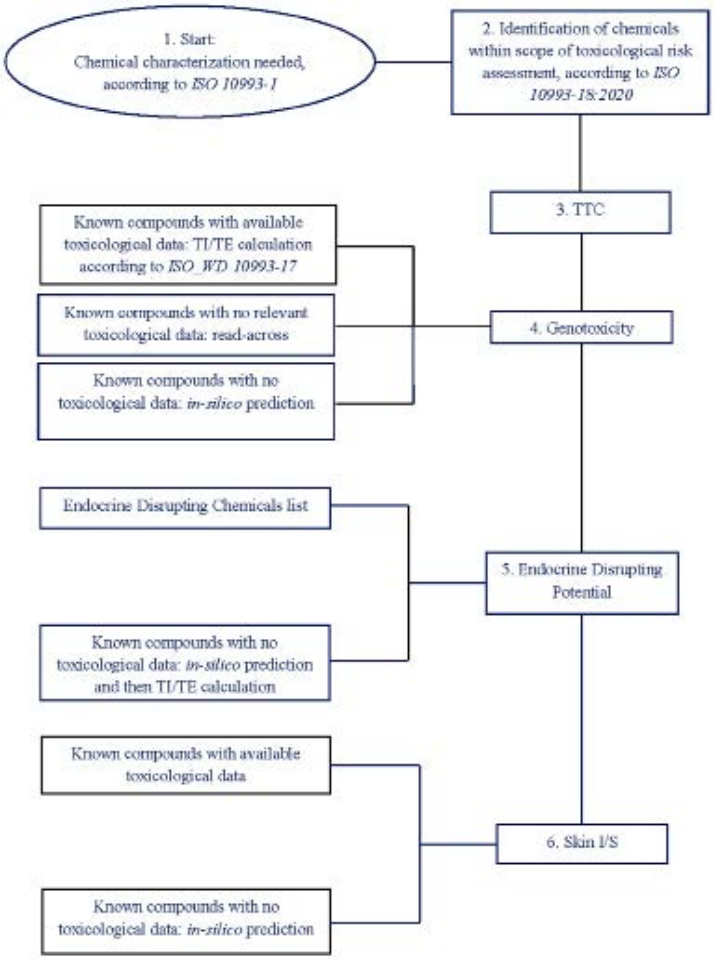
- If there are sufficient toxicological data for the known compounds found during the chemical characterization of MDs, their toxicological evaluation will confirm/exclude these end-points;
- If there are no toxicological data for the known compounds found during the chemical characterization of MDs, it’s possible to perform an in silico prediction.

Finally, computational methods may also complement in vitro and in vivo toxicity tests to potentially minimize the need for animal testing, reduce the cost and time of toxicity tests, and improve toxicity prediction and safety assessment.

In summary, the proposed ED assessment workflow is in accordance with the guidance for risk assessment of chemicals issued by internationally accepted authorities and organizations and generally requires/recommends that all relevant toxicity data should be considered in the assessment process derived from expert judgement in the identification and evaluation of pertinent data[19], [20].

The proposed process is summarized in Figure 1.

Figure 1 - Summary of the proposed workflow.



Conclusions

The proposed workflow, in accordance with accepted regulatory standards, is demonstrated to be a valid and accurate tool for the rigorous evaluation of potential EDCs released during the chemical characterization of MDs. Moreover, it is coordinated well with known available toxicological data and appropriate computational methods for the prediction of chemical toxicity both with endocrine disrupting potential and local end-points such as skin irritation, corrosion and sensitization, in particular, during the conditions of use.

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