CHemical RISk calculators (CHRIS) – Bulk Chemicals (v2)

Catalog of Regulatory Science Tools to Help Assess New Medical Devices

Technical Description

The CHemical RISk calculator (CHRIS) – Bulk Chemicals (version 2) is a tool that enables users to conduct screening level risk assessments to aid in the biocompatibility evaluation of bulk additives and impurities in polymeric medical device components, excluding color additives. These assessments can assist device manufacturers by providing immediate feedback on whether the presence of the bulk chemical would require additional justification and/or testing to demonstrate acceptable biological risk in premarket regulatory review.

The principle of operation relies on first establishing a model to predict exposure limited only by the diffusive transport of the chemical through the polymer matrix. The model is parameterized using a constitutive model for diffusion coefficient (D) as a function of molecular weight (Mw) of the chemical. After segmenting polymer matrices into 8 distinct categories, upper bounds on D(Mw) were determined based on available data for each category. The upper bounds and exposure predictions were validated independently to provide conservative exposure estimates. Then, the exposure estimate is compared to an appropriate threshold of toxicological concern (TTC). The output of the tool is a conservative margin of safety (MOS = TTC ÷ exposure dose) value for a bulk chemical contained within a polymeric medical device component. Based on the MOS value, the calculator determines if further assessment of one or more biocompatibility endpoints is necessary for the specific chemical. Because the toxicological safety limit approach is based on systemic toxicity, CHRIS – Bulk Chemicals (v2) can address acute systemic toxicity, subacute/subchronic toxicity, genotoxicity, carcinogenicity, and reproductive and developmental toxicity.

The CHRIS – Bulk Chemicals (v2) incorporates more accurate (yet still conservative) models, addresses more polymers, and removes the limitation on the solute molecular weights that can be considered when compared to the CHRIS – Bulk Chemicals (v1),.

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Intended Purpose

This calculator provides clinically relevant, yet still conservative, exposure dose estimates using a physics-based transport model for polymeric systems where transport data are available to support the use of the model. The model applies worst-case boundary conditions for release of a substance from the polymer matrix and is based on five primary assumptions:

- The clinical use environment does not cause the polymer matrix to swell or degrade.
- Manufacturing processes do not impact the stability of the polymer.
- The chemical is homogeneously distributed throughout the polymer.
- The total amount of the chemical is present in dilute concentrations (≤ 2 m/v %).
- Any particles/aggregates of the chemical present in the polymer are much smaller than the smallest component dimension (≤ 50x).

While these assumptions are typically valid for bulk additives and impurities in biostable polymers, the user must confirm conformance to the underlying assumptions or provide supporting justification to ensure compliance for a given system. Further, this calculator only enables system specific exposure estimates for 53 polymeric systems that are generally biostable (non-swelling and non-degrading). To estimate chemical release based on the model, the diffusion coefficient of the chemical in the polymer matrix must be specified. For the 53 polymeric systems, a worst-case (upper bound) diffusion coefficient, as a function of molecular weight, has been established based on data from the literature. For polymer matrices that are not included in this list, the bulk chemical risk calculator assigns an ultra-conservative diffusion coefficient that assumes the polymer has the properties of water.

Additional information is available on the Context of Use and Supplemental Publication Information.

Testing

CHRIS – Bulk Chemicals (v2) was developed to provide screening level toxicological risk assessments that are protective, not predictive. The rate of release of extractable compounds has been measured under laboratory conditions that favor maximum release rates [1], and these measured release rates were compared with the predicted rate from the tool. The testing demonstrated that the tool overestimates the rate of exposure by 100-10000x compared with the rates observed under the worst-case experimental conditions and as such provides a very conservative approach to determining exposure and margins of safety. The new upper bounds on D(Mw) in reference [3] were derived using a similar approach as reference [1] but with more than 5x the amount of experimental diffusion data, which allowed the creation of more accurate yet still conservative bounds that address more polymers and solutes. These new bounds demonstrate a similar level of conservatism as the previous bounds, that is, they overestimate exposure by 100-10000x.

Details provided in:

- Saylor, D. M., Chandrasekar, V., Simon, D. D., Turner, P., Markley, L. C., & Hood, A. M. (2019). Strategies for rapid risk assessment of color additives used in medical devices. *Toxicological Sciences*, 172(1), 201-212. https://doi.org/10.1093/toxsci/kfz179
- Saylor, D. M., Chandrasekar, V., Elder, R. M., & Hood, A. M. (2020). Advances in predicting patient exposure to medical device leachables. *Medical Devices & Sensors*, 3(1), e10063. https://doi.org/10.1002/mds3.10063
- Elder, R. M., Saylor, D. M. (2023). Robust estimates of solute diffusivity in polymers for predicting patient exposure to medical device leachables. *Journal of Polymer Science*, available online. https://doi.org/10.1002/pol.20230219

Note: After the publication of reference [3], additional data were located that justify the inclusion of several additional polymer matrices: poly(methyl acrylate) [4-10], poly(ethyl acrylate) [8, 9, 11], poly(butyl acrylate) [9, 12, 13], poly(ethyl cyanoacrylate) [14], poly(butyl cyanoacrylate) [14], and poly(hexyl cyanoacrylate) [14].

Additionally, the upper bounds on D(Mw) using the 95th percentile of the data, were recalculated in place of the statistical procedure in reference [3]. That statistical procedure incorrectly assumes a normal distribution. Using the percentile is a robust, distribution-independent method to ensure the upper bounds are protective.

Limitations

- The tool only addresses compounds with a distribution that is macroscopically homogeneous within the matrix. Therefore, only compounds that are introduced either intentionally or unintentionally during synthesis (such as residual monomers and oligomers, catalysts, initiators) or compounding (such as stabilizers, antioxidants, plasticizers) are within scope. Surface residuals from processing, cleaning, and sterilization are excluded.
- The tool requires the total amount of the chemical to be established in advance, e.g., based on a certificate of analysis.
- The tool only addresses individual chemicals; therefore, a favorable outcome by the tool does not imply acceptable biological risk for the final finished form of a medical device.
- The tool cannot be used to screen the potential risk of polymer medical device components that contact the body by the inhalation route.
- Under the information (i) icon button next to Device characteristics, the discussion of 'Exposure type' states that, "≤ 24 hours = limited. For limited exposures (≤ 24 hours), please enter the maximum exposure time in hours." For additional information on device contact classification, it is recommended that users refer to the FDA's Biocompatibility Guidance for current thinking on how to determine the device's contact classification or exposure type.

- The tool excludes color additives. For color additives, use the CHRIS – Color Additives (v1) or CHRIS – Color Additives (v2).
- The tool does not address metals (for example, barium atoms). The tool treats ceramics (for example, silica or alumina) as insoluble particles and assigns them a conservative molecular weight (1100 g/mol).

Supporting Documentation

- CHemical RISk calculator (CHRIS) – Bulk Chemicals (version 2) Context of Use
- Supplemental Publication Information
    - Saylor, D. M., Chandrasekar, V., Simon, D. D., Turner, P., Markley, L. C., & Hood, A. M. (2019). Strategies for rapid risk assessment of color additives used in medical devices. *Toxicological Sciences*, 172(1), 201-212. https://doi.org/10.1093/toxsci/kfz179
    - Saylor, D. M., Chandrasekar, V., Elder, R. M., & Hood, A. M. (2020). Advances in predicting patient exposure to medical device leachables. *Medical Devices & Sensors*, 3(1), e10063. https://doi.org/10.1002/mds3.10063
    - Elder, R. M., Saylor, D. M. (2023). Robust estimates of solute diffusivity in polymers for predicting patient exposure to medical device leachables. *Journal of Polymer Science*, available online. https://doi.org/10.1002/pol.20230219
    - H. Fujita, A. Kishimoto, K. Matsumoto, Concentration and temperature dependence of diffusion coefficients for systems polymethyl acrylate and n-alkyl acetates. *Transactions of the Faraday Society,* **56**, 424-437 (1960). https://doi.org/10.1039/TF9605600424
    - Kishimoto, E. Maekawa, H. Fujita, Diffusion Coefficients for Amorphous Polymer and Water Systems. *Bulletin of the Chemical Society of Japan,* **33**, 988-992 (1960). https://doi.org/10.1246/bcsj.33.988
    - W. H. Burgess, H. B. Hopfenberg, V. T. Stannett, Transport of noble gases in poly(methyl acrylate). *Journal of Macromolecular Science, Part B* **5**, 23-40 (1971). https://doi.org/10.1080/00222347108212519
    - J. S. Chiou, J. W. Barlow, D. R. Paul, Sorption and transport of gases in miscible poly(methyl acrylate)/poly(epichlorohydrin) blends. *Journal of Applied Polymer Science,* **30**, 1173-1186 (1985). https://doi.org/10.1002/app.1985.070300322
    - Z. Mogri, D. R. Paul, Gas sorption and transport in poly(alkyl (meth)acrylate)s. II. Sorption and diffusion properties. *Polymer,* **42**, 7781-7789 (2001). https://doi.org/10.1016/S0032-3861(01)00260-9
    - S. Maji, O. Urakawa, K. Adachi, Relationship between segmental dynamics and tracer diffusion of low mass compounds in polyacrylates. *Polymer,* **48**, 1343-1351 (2007). https://doi.org/10.1016/j.polymer.2006.12.039
    - D. W. Janes, J. S. Kim, C. J. Durning, Interval Sorption of Alkyl Acetates and Benzenes in Poly(methyl acrylate). *Industrial & Engineering Chemistry Research* **52**, 8765-8773 (2013). https://doi.org/10.1021/ie300536c

- Kishimoto, Y. Enda, Diffusion of benzene in polyacrylates. *Journal of Polymer Science Part A: General Papers,* **1**, 1799-1811 (1963). https://doi.org/10.1002/pol.1963.100010530
- J. Li, K. D. Sullivan, E. B. Brown, M. Anthamatten, Thermally activated diffusion in reversibly associating polymers. *Soft Matter,* **6**, 235-238 (2010). https://doi.org/10.1039/B909662K
- G. S. Sheridan, C. M. Evans, Understanding the Roles of Mesh Size, Tg, and Segmental Dynamics on Probe Diffusion in Dense Polymer Networks. *Macromolecules,* **54**, 11198-11208 (2021). https://doi.org/10.1021/acs.macromol.1c01767
- W. R. Vezin, A. T. Florence, Diffusion of Small Molecules in Amorphous Polymers. *Journal of Pharmacy and Pharmacology,* **29**, 44P-44P (1977). https://doi.org/10.1111/j.2042-7158.1977.tb11512.x

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Tool Reference

In addition to citing relevant publications please reference the use of this tool using DOI: 10.5281/zenodo.8383585

For more information:

- Catalog of Regulatory Science Tools to Help Assess New Medical Devices