MDDT SUMMARY OF EVIDENCE AND BASIS OF QUALIFICATION DECISION FOR CHEMICAL RISK CALCULATOR (CHRIS) – COLOR ADDITIVES

BACKGROUND

MDDT NAME: CHEMICAL RISK CALCULATOR (CHRIS) – COLOR ADDITIVES
SUBMISSION NUMBER: U210555
DATE OF SUBMISSION: DECEMBER 14, 2021
CONTACT: David M. Saylor, PhD
OFFICE OF SCIENCE AND ENGINEERING LABORATORIES
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
U.S. FOOD AND DRUG ADMINISTRATION
10903 NEW HAMPSHIRE AVENUE
SILVER SPRING, MD 20993
PHONE: 301-796-2626
DAVID.SAYLOR@FDA.HHS.GOV

TOOL DESCRIPTION AND PRINCIPLE OF OPERATION

CHemical RISk calculator (CHRIS) – Color Additives is a Nonclinical Assessment Model (NAM) to conduct screening level risk assessments to aid in the biocompatibility evaluation of polymeric medical device components that contain color additives (CAs). The principle of operation relies on first derivation of tolerable intake values and then establishment of a model to predict exposure limited only by the diffusive transport of the additive 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 color additive. After segmenting polymer matrices into 4 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 estimates. Because both components (toxicity and exposure) are conservative, a ratio of tolerable intake to exposure in excess of one indicates acceptable risk.[1]

In the absence of adequate toxicological and exposure data for a CA (or associated additives and impurities) in a polymeric matrix, a toxicological risk assessment can be conducted for systemic biocompatibility endpoints by comparing the total amount of a CA, associated additive, or impurities in the matrix to an appropriate threshold of toxicological concern (TTC). This is the approach used by CHRIS – Color Additives in the absence of exposure and toxicity data for a particular system. For the CAs listed below in Table 1, CHRIS – Color Additives applies a CA-specific toxicological threshold value called a tolerable intake (TI) value. These TIs are based on available systemic (including reproductive / developmental, genotoxicity, and carcinogenicity) toxicity data. Because both the TTC and TI approaches are based on systemic toxicity, CHRIS – Color Additives can address acute systemic toxicity, subacute/subchronic toxicity, genotoxicity, carcinogenicity, and reproductive and developmental toxicity.

It does not, however, address cytotoxicity, sensitization, irritation, hemocompatibility, material mediated pyrogenicity, or implantation. Therefore, an MOS >= 1 implies the CA will not raise a safety concern with respect to only the systemic biocompatibility endpoints, which is reflected in the output of CHRIS – Color Additives.

The qualified tool is CHRIS – Color Additives v1.1. The report it generates includes the date and version number. The landing page also includes a changelog. (https://chris-osel.pythonanywhere.com)

QUALIFIED CONTEXT OF USE

The CHemical RISk calculator (CHRIS) – Color Additives is qualified to conduct screening level risk assessments to aid in the biocompatibility evaluation of polymeric medical device components that contain color additives (CAs) (see Note 1 below).

CHRIS – Color Additives can aid in the biocompatibility evaluation of following biocompatibility endpoints: acute systemic toxicity, subacute/subchronic toxicity, genotoxicity, carcinogenicity, and reproductive and developmental toxicity. It does not, however, aid in the biocompatibility evaluation of cytotoxicity, sensitization, irritation, hemocompatibility, material mediated pyrogenicity, or implantation. Therefore, an MOS >= 1 implies the CA will not raise a safety concern with respect to only the systemic biocompatibility endpoints, which is reflected in the output of CHRIS – Color Additives.

While the calculations and methods discussed in this context of use produce conservative estimates, some caveats remain. These caveats are discussed in the 'Assessment of Advantages/Disadvantages of Qualification' section of the 'Summary of Evidence to Support Qualification'.

Note 1: The term "color additive", as defined under section 201(t) of the FD&C Act, means a material which:

> "is a dye, pigment, or other substance made by a process of synthesis or similar artifice, or extracted, isolated, or otherwise derived, with or without intermediate or final change of identity, from a vegetable, animal, mineral, or other source, and when added or applied to a food, drug, or cosmetic, or to the human body or any part thereof, is capable (alone or through reaction with other substance) of imparting color thereto; except that such term does not include any material which the Secretary [of the Department of Health and Human Services] by regulation, determines is used (or intended to be used) solely for a purpose or purposes other than coloring."

SUMMARY OF EVIDENCE TO SUPPORT QUALIFICATION

The Chemical Risk Calculator – Color Additives tool was developed to provide screening level toxicological risk assessments that are protective, not predictive. The rate of release of specific CAs 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 protective approach is demonstrated in Figure 11 below, which compares the fractional mass release of 4 specific CAs (y-axis) against a normalized measure of time. It can be clearly seen that the tool equation (black line below) is protective under all conditions with these CAs.

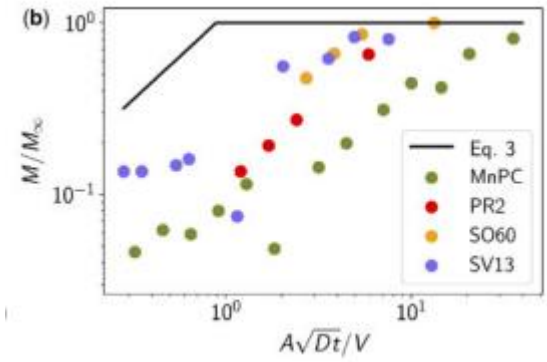

Figure 1

The results of this testing validate the tool's ability to provide assurance of the safety of the use of a specific CA when used within the qualified Context of Use.

Toxicological profiles were collected for eleven (11) CAs commonly used in medical devices, and TIs were derived for the eleven (11) CAs in ***Table 1.*** The profiles included physicochemical structure and properties, hazard identification, and dose-response assessment.

Table 1: Color Additives		
	Color Additive	**CAS #**
1	Titanium dioxide	13463-67-7
2	Carbon black	1333-86-4
3	Pigment brown 24	68186-90-3
4	Zinc Oxide	1314-13-2
5	Pigment Red 101	1309-37-1
6	Solvent violet 13	81-48-1
7	Manganese phthalocyanine	14325-24-7
8	Pigment blue 15	147-14-8
9	Phthalocyanine green	1328-53-6
10	Ultramarine blue	57455-37-5
11	Pigment Yellow 138	30125-47-4

CHRIS – Color Additives applies worst-case boundary conditions for release of a substance from the polymer matrix and is based on four (4) primary assumptions:

- The polymer does not swell or degrade in-vivo, nor does the presence of CA impact the integrity of the polymer.
- The total amount of CA is present in dilute concentrations (<= 2 % m/v) within the colored component.
- The CA is homogeneously distributed throughout the polymer.
- The smallest dimension of the colored device component is much greater than the size of any color additive particles that may be present (<= 50x).

Users of CHRIS – Color Additives must confirm validity of the aforementioned underlying assumptions or provide supporting justification to ensure compliance for a given polymer-color additive system. Further, CHRIS – Color Additives only enables system specific exposure estimates for nineteen (19) polymeric systems that are generally biostable (non-swelling and non-degrading) and contain less than 2% m/v of a given CA. These polymers are listed below.

Table 2. Polymeric Systems	
1	Silicone
2	Polyethylene (density <= 0.94 g/cm3)
3	Polyethylene (density > 0.94 g/cm3)
4	Polyethylene terephthalate
5	Polyurethane (polyether)
6	Polycarbonate
7	Polyoxymethylene
8	Poly(methyl methacrylate)
9	Acrylonitrile butadiene styrene
10	Polyether block amide
11	Polyamide *
12	Polystyrene
13	Polyvinyl chloride
14	Polytetrafluoroethylene
15	Polypropylene
16	Polyvinyl acetate
17	Polybutylene terephthalate (PBT) *
18	Polyetheretherketone (PEEK) *
19	Fluorinated ethylene propylene (FEP) *
* See additional notes below on these specific polymeric systems	

Additional information for polyamide, polybutylene terephthalate (PBT), polyethereketone (PEEK), fluorinated ethylene propylene (FEP) was reviewed and summarized below along with an approach for certain “unlisted polymer” systems. This additional information is summarized below.

Polymeric System	11. Polyamides (PA)
Note	The data for polyamides was based on leaching studies conducted in nonaqueous media such as olive oil and isooctane.[2] Some polyamides, such as nylon 12 can undergo limited plasticization due to the presence of absorbed water. Therefore, to ensure the exposure predictions remain conservative, polyamides were categorized as “plastics II” instead of “glass” to account for the potential plasticization due to water uptake in physiologically relevant media.
Reference	[2] Hoekstra, E. J.; Brandsch, R.; Dequatre, C.; Mercea, P.; Milana, M.; Stormer, A.; Trier, X.; Vitrac, O.; Schafer, A.; Simoneau, C. Practical Guidelines on the Application of Migration Modelling for the Estimation of Specific Migration; Publ Off Eur Union., 2015 and references therein

Polymeric System	17. Polybutylene terephthalate (PBT)
Note	Similar to PEEK, no specific diffusion data in the literature for additives in the size range of interest (100 g/mol < Mw < 1100 g/mol) were located. However, PBT is a semi-aromatic polyester similar in structure and properties to two matrices with direct measurements of D available in the literature that are listed in the manuscript, polyethylene terephthalate (PET) and polyethylene naphthalate (PEN). Based on these similarities in structure and properties, PBT should fall well within the glass category.

Polymeric System	18. Polyetheretherketone (PEEK)
Note	Specific diffusion data was unavailable in the literature for additives in the size range of interest (100 g/mol < Mw < 1100 g/mol) for PEEK. However, to categorize PEEK matrices it has been recognized that the glass transition temperature is well in excess of body temperature at around 143 °C and the density is 1.3 g/cm3. Based on materials with comparable structure and properties, it should fall well within the glass category, which is bounded by the diffusion behavior of unswollen polyamides (nylon 12, specifically).

Polymeric System	19. Fluorinated ethylene propylene (FEP)
Note	There are limited direct measurements of D for FEP matrices. Measurements of benzene diffusion at 45 °C suggest the diffusion behavior will be well within the plastics II category[3]. Larger molecule diffusion data are only available at 70 °C [4]. However, even at this substantially elevated temperature, the upper bounds for the plastics II category are within a factor of 2 of the direct D measurements. Further, FEP is similar in structure and has similar gas and liquid barrier properties as PTFE[5], which was established as a plastics II matrix. Given the level of supporting evidence, FEP has been elected to be categorized as a plastics II polymer.
Reference	[3] S. Lee, K.S. Knaebel, Effects of mechanical and chemical properties on transport in fluoropolymers. I. Transient sorption, J. Appl. Polym. Sci. 64 (1997) 455–476. [4] M.S. Hedenqvist, J.E. Ritums, M.C. Brana, G. Bergman, Sorption and desorption of tetrachloroethylene in fluoropolymers: Effects of the chemical structure and crystallinity, J. Appl. Polym. Sci. 87 (2003) 1474–1483. [5] van Weeren, R, DJ Gibboni. 2002. “Barrier Packaging as an Integral Part of Drug Delivery,” Drug Development & Deliver, vol. 2, no. 4, (June 2002).

Polymeric System	Unlisted polymers
Note	Because this category can potentially encompass polymers such as hydrogels, which contain high concentrations of water, as a worst-case scenario, it was assumed that the polymer matrix has the properties of liquid phase water at 37 °C. As a conservative estimate, D as a function of the Mw of an additive was established based on the predicted diffusion of linear alkanes according to the Wilke-Chang model for liquid phase diffusion in water at 37 °C.[6]
Reference	[6] C.R. Wilke, P. Chang, Correlation of diffusion coefficients in dilute solutions, AIChE Journal.1 (1955) 264–270.

DISCUSSION OF THE STRENGTH OF EVIDENCE TO SUPPORT QUALIFICATION

The objective in the development of CHRIS is to provide assessments that are protective, not predictive. The result is a tool that remains as protective (or more so) compared to the current biocompatibility or chemical characterization testing based on order of magnitude, physics-based arguments.

To accomplish this, orders of magnitude of conservatism have been built into the assessment. For example, upper bounds on diffusion coefficients (D) have been used that are based on measurements made on entire categories of polymers that encompass a wide range of chemistries and process histories. Thus, the D value used for a typical CA system will be overestimated by multiple orders of magnitude.

Further, in the vast majority of device relevant systems, the limited solubility of the CA in the polymer will further reduce the (effective) D by additional orders of magnitude in actual systems.

Finally, implementing a sink condition at the device-tissue interface in the model overestimates actual release in all but the most rapid flow conditions, where no substantive boundary layer is able to develop at that interface. In addition to these exposure considerations, the toxicological assessments also incorporate several orders of magnitude of conservatism in the form of uncertainty factors to account for uncertainty in derivation of the TI/chemical safety threshold and assume worst-case exposure route and duration.

Therefore CHRIS – Color Additives can be used to conduct a screening level risk assessment to aid in biocompatibility evaluation of polymeric medical device components that contain color additives.

The improved clinical relevance of the tool, compared to chemical analysis data and subsequent toxicological risk assessment, derives from the use of a physics-based model, which uses the total amount of CA provided by the user that can be present in the polymer as a basis. Conversely, chemical analysis data is generated using solvents that can dramatically either overestimate or underestimate clinical exposure. Moreover, exposure predictions provided by CHRIS will remain protective due to the factors detailed above, but summarized here: physics-based overestimation of diffusion, wide range of published chemical analysis data, worst-case assumptions regarding the peri-implant environment, and limited solubility of CA.

ASSESSMENT OF ADVANTAGES/DISADVANTAGES OF QUALIFICATION

The tool has advantages of ease of use and possibly reducing the testing needed for Color Additive containing medical devices.

These assessments can assist device manufacturers by providing instantaneous feedback on whether the presence of CAs or other additives and impurities associated with CAs in a device would require additional justification and/or testing to demonstrate acceptable biological risk.

CHRIS – Color Additives 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 user is cautioned to read the instructions very carefully and follow them in detail. To estimate CA release based on the model, the diffusion coefficient of the CA in the polymer matrix must be specified. For the nineteen (19) listed polymeric systems, a

worst-case (upper bound) diffusion coefficient, as a function of additive molecular weight, has been established based on data from the literature. For polymer matrices that are not included in this list, CHRIS – Color Additives assigns an ultra-conservative diffusion coefficient that assumes the polymer has the properties of water. (Since polymers never behave as 'fluid' as water)

CHRIS – Color Additives only addresses CAs, therefore a favorable outcome by CHRIS – Color Additives does not imply a complete acceptable biological risk assessment for the final finished form of a medical device. CHRIS – Color Additives is also not intended to establish device classification or identify biocompatibility requirements

The following disadvantages, and limitations remain:

1. CHRIS – Color Additives cannot be used to screen the potential risk of polymer medical device components that contact the body by the inhalation route.
2. The worst-case diffusion coefficient is only defined over a molecular weight range of 100 to 1100 g/mol. This tool is still applicable for substances with a molecular weight > 1100 g/mol since larger molecules diffuse slower than smaller molecules and have smaller diffusion coefficients. CHRIS – Color Additives currently cannot be used to estimate exposure for substances with a molecular weight < 100 g/mol.
3. 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.
4. Some of the color additives listed in the CHRIS tool are not all listed under 21 CFR 73 Subpart D and 21 CFR 74 Subpart D as color additives appropriate to use in medical devices for additional information on appropriate use of CAs it is recommended that users refer to the device specific guidances, and what is allowed per the CFR.

CONCLUSIONS

Based on the evidence provided, this non-clinical assessment model MDDT "Chemical RISk calculator" is qualified within its context of use as well as the advantages and disadvantages indicated above.

CONTACT INFORMATION FOR ACCESS TO TOOL

The qualified version CHRIS – Color Additives v 1.1 is posted on following URL https://chris-osel.pythonanywhere.com. It is publicly available at this address. Further information can be requested from David Saylor: david.saylor@fda.hhs.gov.

REFERENCES

1) David M. Saylor, Vaishnavi Chandrasekar, David D. Simon, Paul Turner, Laura C. Markley, and Alan M. Hood, *Toxicological Sciences*, 172(1), 2019, 201–212
2) Hoekstra, E. J.; Brandsch, R.; Dequatre, C.; Mercea, P.; Milana, M.; Stormer, A.; Trier, X.; Vitrac, O.; Schafer, A.; Simoneau, C. Practical Guidelines on the Application of Migration Modelling for the Estimation of Specific Migration; Publ Of Eur Union., 2015 and references therein
3) S. Lee, K.S. Knaebel, Effects of mechanical and chemical properties on transport in fluoropolymers. I. Transient sorption, *J. Appl. Polym. Sci*. 64 (1997) 455–476.
4) M.S. Hedenqvist, J.E. Ritums, M.C. Brana, G. Bergman, Sorption and desorption of tetrachloroethylene in fluoropolymers: Effects of the chemical structure and crystallinity, *J. Appl. Polym. Sci*. 87 (2003) 1474–1483.
5) van Weeren, R, DJ Gibboni. 2002. “Barrier Packaging as an Integral Part of Drug Delivery,” *Drug Development & Deliver*, vol. 2, no. 4, (June 2002).
6) C.R. Wilke, P. Chang, Correlation of diffusion coefficients in dilute solutions, *AIChE Journal.*1 (1955) 264–270.