Hazard Identification of Printing Ink Substances Used on the Exterior of Food Packaging

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Abstract

Photoinitiators are molecules that create reactive species when exposed to radiation and are widely used in UV-cured printing inks applied to the exterior of food contact materials (e.g., coatings and varnishes). New data indicates that, for some intended uses, photoinitiators applied to the exterior of food packaging may migrate to food. The purpose of this project is to perform hazard characterization of ~100 photoinitiators used in printing ink substances for food packaging. A new approach methodology (NAM) was applied using the ChemTunes-ToxGPS database and in silico workflows to determine the Cramer classification and genotoxicity predictions for each of the identified photoinitiators. The Cramer Decision Tree (CDT) uses chemical structure and predicted chemical reactivity of a substance to categorize substances into three classifications with Class III substances representing the highest predicted toxicological hazard. Based on the Cramer classifications and predicted genotoxicity, the photoinitiators were characterized and prioritized for further analysis to identify existing toxicity data in FDA's Chemical Evaluation and Risk Estimation System (CERES) and available literature. This analysis helped determine those photoinitiators that may need further investigation for their intended use, potential migration into food, and possible consideration for further regulation. This qualitative hazard identification approach supports the Agency's mission of incorporating the 3 R's into safety assessments (i.e., Replacement, Reduction, and Refinement) for promoting ethical research, testing, and education using animals. Future work will be to use this NAM approach to characterize and prioritize an estimated >5,000 ink substances and ink components potentially used in printing inks applied on the exterior of food packaging in U.S. markets.

Introduction

- UV printing inks applied to the exterior of food contact materials (e.g., coatings/ varnishes) are comprised of four major components: monomers, oligomers, pigments, and photoinitiators.
- Photoinitiators are activated by UV radiation and create reactive species that can initiate polymerization processes.
- New data indicates that, for some intended uses, photoinitiators applied to the exterior of food packaging may migrate to food (Figure 1).
- Project Aims:
  - Identify photoinitiators potentially used in printing ink substances on the exterior of food packaging on U.S. markets
  - Determine the Cramer classification and genotoxicity and tumorgenicity predictions for each photoinitiator
  - Prioritize printing inks substances by identifying those that may be of higher concern

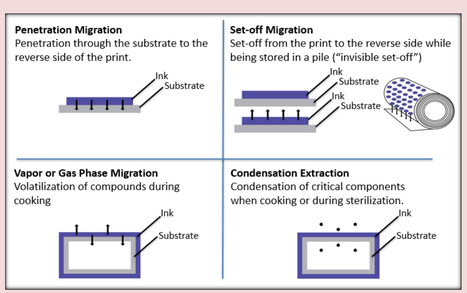

Figure 1. Possible Migration Scenarios for Photoinitiators

Materials and Methods

- We determined 106 photoinitiators are potentially used in printing inks applied to the exterior of food packaging in U.S. markets.
- We established if the photoinitiator had a CASRN and a Cramer class value using the Threshold of Toxicological Concern (TTC)
- For each photoinitiator, Cramer classifications (revised) and genotoxicity predictions were determined using the ChemTunes-ToxGPS* database and in silico workflows.
  - CDT uses chemical structure and predicted chemical reactivity of a substance to categorize substances into three classifications with associated Threshold of Toxicological Concern (TTC) values (Table 1).
  - Genotoxicity predictions were determined from global model and local statistical QSAR models and chemical structural alerts and included the bacterial reverse mutation test (or Ames test), in vitro chromosomal aberration assay and the in vivo micronucleus assay.

Table 1: CDT Classifications and TTC Values

CDT Classification	TTC value (µg/person/day)	TTC value (µg/kg bw/d)
Potential DNA-reactive mutagens and/or carcinogens	0.15	0.0025
Organophosphates and carbamates	18	0.3
Cramer Class III	90	1.5
Cramer Class II	540	9.0
Cramer Class I	1,800	30

*ChemTunes Database and ToxGPS Predictions are available at https://www.ceres.chemtunes.com/ provided by ChemTunes•ToxGPS® v3.2020, MN-AM (Molecular Networks Altamira), Nuremberg, Germany and Columbus, OH, USA. www.mn-am.com.

- We searched various databases (FARM, CERES, Appian-TEMPO, ChemIDPlus, Pubmed/PubChem, SciFinder, Google, ECHA, EPA Comptox Dashboard, IARC, NTP) using CASRN and/or name(s) of photoinitiators for in vitro and in vivo toxicological data.
  - Reported negative/positive results were recorded from the in vitro genotoxicity studies.
  - Reported point-of-departures (POD) were recorded from the in vivo toxicological studies.
  - Two-year carcinogenesis studies (and/or unit cancer risk values) were denoted for determination of putative human carcinogens.
- Prioritization ranking for each photoinitiator was determined using a weight-of-evidence (WoE) approach with designations of low, medium or high (Figure 2).
  - Prioritization is aimed at identifying substances that may be of higher concern and is not intended as replacement of the actual risk assessment. Substances with higher priority do not necessarily pose a higher health risk than substances of lower priority.

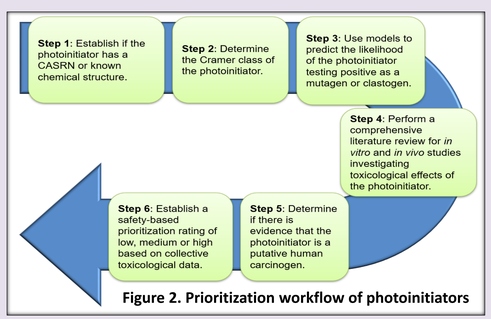

Figure 2. Prioritization workflow of photoinitiators

Results and Discussion

- 97 photoinitiators had known CASRNs and were analyzed in ChemTunes-ToxGPS.
- CDT classifications were 6 photoinitiators identified as Class 1, 10 identified as Class 2, and 37 identified as Class 3 (Table 2).
  - 1 substance was identified as a cohort of concern, which was erbium oxide sulfide (CASRN 12345-97-0).
  - 43 substances were deemed not appropriate for Cramer Class identification.
- The genotoxicity predictions:
  - 10 photoinitiators were predicted positive in the Ames test and were further analyzed in Table 3.
  - 41 photoinitiators were predicted negative in the Ames test.
- A comprehensive literature search was conducted for further toxicological data on the 10 photoinitiators predicted positive in the Ames test (Table 3).
  - Using a WoE approach to determine prioritization ranking, eight of the photoinitiators were given a ranking of high, and two were given a ranking of medium.
- The prioritization rankings for the complete 106 photoinitiators include 44 substances being a low ranking, 26 substances having a medium ranking, and 36 substances having a high ranking.
- Future work will include performing a comprehensive literature search for the remaining photoinitiators that received a high prioritization ranking.

Table 3. CDT Classifications, Mutagenicity/Clastogenicity Test Results and Prioritization Ranking for Photoinitiators Predicted Positive for Ames Test

			Mutagenicity		Clastogenicity					
Photoinitiators Predicted Positive for the Ames Test	CASRN	Cramer Class	Predicted Ames	Ames Test*	Predicted In Vitro Chrom Ab	In Vitro Chrom Ab Assay*	Predicted In Vivo MN	In vivo MN Assay*	NOAEL* (mg/kg-day)	Prioritization Ranking
Anthraquinone, 2-ethyl-	84-51-5	Class III	positive	negative	positive	positive	negative	negative	none	High
Benzophenone, 4,4'-bis(diethylamino)-	90-93-7	Class III	positive	negative	uncertain	none	negative	none	none	High
Glyoxylic acid, phenyl-, ethyl ester	1603-79-8	Class I	positive	none	uncertain	none	negative	none	none	Medium
Glyoxylic acid, phenyl-, methyl ester	15206-55-0	Class I	positive	negative	positive	negative (in vitro MN)	positive	none	1000 (Reprod/Dev tox study-rat)	High
Anthracene, 9,10-dibutoxy	76275-14-4	Class III	positive	none	positive	none	negative	none	none	High
1-Butanone, 2-(dimethylamino)-1-[4-(4- morpholinyl)phenyl]-2-(phenylmethyl)-	119313-12-1	Class III	positive	negative	negative	negative (MLA assay)	negative	none	none	Medium
1-Butanone, 2-(dimethylamino)-2-[(4- methylphenyl)methyl]-1-[4-(4-morpholinyl)phenyl]-	119344-86-4	Class III	positive	negative	negative	negative	negative	none	60 (Reprod/Dev tox study-rat)	High
4,4'-Bis(methylethylamino) benzophenone	194655-98-6	Class III	positive	none	positive	none	negative	none	none	High
Mixture of Oxy-phenyl-acetic acid 2-[2-oxo-2-phenyl- acetoxy-ethoxy]-ethyl ester and Oxy-phenyl-acetic 2-[2- hydroxy-ethoxy]-ethyl ester	211510-16-6	Class III	positive	none	uncertain	none	negative	none	none	High
Mixture of Oxy-phenyl-acetic acid 2-[2-oxo-2-phenyl- acetoxy-ethoxy]-ethyl ester and Oxy-phenyl-acetic 2-[2- hydroxy-ethoxy]-ethyl ester	442536-99-4	Class III	positive	none	uncertain	none	negative	none	none	High

* Note: Study results are reported by the study author and have not been fully reviewed by this Reviewer.

Table 2: Collective Cramer Decision Tree Classifications and Predicted Genotoxicity Test Results of Photoinitiators

Cramer Class	Number of Photoinitiators	Predicted GT call	Predicted Ames	Predicted In Vitro Chrom Ab	Predicted In Vivo MN
Class 1	6	Negative	4	0	5
		Positive	2	2	1
Class 2	10	Negative	9	2	9
		Positive	0	4	0
Class 3	37	Negative	28	14	25
		Positive	8	7	11
Cohort of Concern	1	Negative	1	0	0
		Positive	0	0	1
Not appropriate for CDT	43	Negative	1	0	1
		Positive	0	1	0

Abbrev- CDT: Cramer Decision Tree; Chrom Ab: Chromosomal Aberration Assay; GT: Genotoxicity; MN: Micronucleus Assay. Cohort of Concern- Five "structural groups" are excluded from TTC: potent carcinogen (nitroso, azoxy, aflatoxin-like) or strongly bioaccumulating (polyhalogenated dibenzodioxins/benzofurans and steroids).

Conclusion

- Safety-based prioritization rankings were determined for photoinitiators potentially used in printing inks applied to the exterior of food packaging in U.S. markets.
- Rankings were determined by Cramer classification, predicted genotoxicity, and available toxicity data for each photoinitiator.
- Prioritization rankings support determination of photoinitiators that need further investigation for available toxicity data, intended use, potential migration into food, and possible regulation.
- The safety-based prioritization rankings supported the Agency's mission of incorporating the 3 R's into safety assessments (i.e., Replacement, Reduction and Refinement) for promoting ethical research, testing, and education using animals.

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