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Safety assessment for octadecyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-propionate (CAS Reg. No. 2082-79-3) from use in food contact applications

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ABSTRACT

Octadecyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate (CAS Reg. No. 2082-79-3), currently marketed as Irganox 1076 (I-76), is a sterically hindered phenolic antioxidant used in a variety of organic substrates, including those used in the manufacture of food contact articles. In 2012, the US Food and Drug Administration (USFDA), Office of Food Additive Safety (OFAS), initiated a post-market re-evaluation of the food contact applications of I-76. This project aimed to ensure that current dietary exposures from the use of I-76 in food contact articles are accurately captured and the safety assessment considered all relevant and available toxicological information. To accomplish these aims, the USFDA reviewed the available toxicological studies and chemistry information on food contact applications of I-76. Based on this in-depth analysis, a NOAEL of 64 mg/kg-bw/d (female rats) from a chronic rat study and a cumulative estimated dietary intake (CEDI) of 4.5 mg/p/d, was used to calculate a margin of exposure (MOE) of ~850. We concluded that the previous and current exposure levels provide an adequate margin of safety (MOS) and remain protective of human health for the regulated uses.

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1. Background

Octadecyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl) propionate (CAS Reg. No. 2082-79-3; Fig. 1) is a sterically hindered phenolic containing a long aliphatic hydrocarbon chain that is used as an antioxidant in a variety of organic substrates, such as plastics, elastomers, adhesives, waxes, and lubricating oils, including those used in the manufacture of food contact articles. It is a large, high molecular weight (MW~531 g/mol), hydrophobic compound (water solubility <0.01% at 20 °C) with low volatility (vapor pressure 2.5×10^{-7} Pa at 20 °C). It is known by several other chemical names and is currently marketed as Irganox 1076 (I-76).

The original Ciba Specialty Chemical Company (CSCC) patents for I-76 expired years ago and numerous generic versions are now available. As a result, there has been an influx of new regulatory submissions to the Office of Food Additive Safety (OFAS) for new uses of I-76. OFAS recently conducted a post-market safety assessment of I-76 in food contact applications. Under this post-market evaluation, OFAS reviewed the available toxicological studies and chemistry information, including the US regulatory status, uses, and migration levels in food and food simulants. This initiative aimed to ensure that current exposures are accurately captured and the safety assessment considers all relevant toxicological information available since the time of premarket approval.

2. Uses and safety assessment

The food contact uses of I-76 are specified in several regulations in Title 21, Parts 170 through 199, of the Code of Federal Regulations (denoted as 21 CFR §170-199) and several effective food

Abbreviations: ABS, acrylonitrile-butadiene-styrene; ac, acidic; al, alcoholic; aq, aqueous; CDC, cumulative dietary concentration; CEDI, cumulative estimated daily intake; CF, consumption factor; CSCC, Ciba Specialty Chemical Company; DC, dietary concentration; EDI, estimated daily intake; F_1 , first filial generation; F_2 , second filial generation; FAP, food additive petition; FCN, food contact notification; FCS, food contact substance; FFDCA, Federal Food, Drug, and Cosmetic Act; fat, fatty; f_T , food distribution factor; FSL, food simulating liquid; GLP, good laboratory practice; HIPS, high-impact polystyrene; I-76, irganox 1076; LDPE, low-density polyethylene; LLDPE, linear low-density polyethylene; LOAEL, lowest-observed-adverse-effect level; LOEL, lowest-observed-effect level; MFSL, migration value for a food simulating liquid representing a specific food type; Mlbs, million pounds; MOE, margin of exposure; MOS, margin of safety; MW, molecular weight; NOAEL, no-observed-adverse-effect Level; NOEL, no-observed-effect level; OFAS, Office of Food Additive Safety; P_0 , parental generation; PE, polyethylene; PET, poly(ethylene terephthalate); PP, polypropylene; PS, polystyrene; PVC, poly(vinyl chloride); QA, quality assurance; RMPS, rubber modified polystyrene; US FDA, United States Food and Drug Administration.

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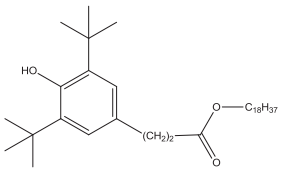

CAS Reg. Name:	Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate
FARM Preferred Name:	Stearyl-3,5-di-tert-butyl-4-hydroxyhydrocinnamate
CAS Reg. No.:	2082-79-3
Common Name:	Irganox 1076
Molecular Weight:	531 g/mol
Melting Range:	50-55 °C
Flashpoint:	273 °C
Solubility (20 °C, % w/w)	Water < 0.01, acetone 19, benzene 57, chloroform 57, cyclohexane 40, ethanol 1.5, ethyl acetate 38, n-hexane 32, methanol 0.6, toluene 50

Fig. 1. Structure and physical/chemical properties of octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate.

contact notifications (FCN). Access to these listings and detailed discussions on the premarket approval process for food contact substances (FCS) are available on USFDA's website (www.fda.gov). With regard to the regulations, I-76 (under its chemical name) is listed specifically in the following regulations: 21 CFR §175.105 (Adhesives), §178.2010 (Antioxidants and/or stabilizers for polymers) and §177.1010 (Acrylic and modified acrylic plastics, semi-rigid and rigid), through a total of 23 food additive petitions (FAPs) submitted and approved prior to 2000. Section 178.2010 is the primary regulation as it contains 14 entries (i.e., Limitations) for specific uses. Of note, Limitation no. 2 in §178.2010(b) provides for the uses under §175.105 and §177.1010(a)(5). In addition, I-76 is the subject of 9 effective FCNs since 2000.

As detailed elsewhere (Bailey et al., 2008; Twaroski et al., 2007), the essence of FDA's safety assessment for FCSs, whether it be for premarket approval or postmarket evaluation, relies on evaluating dietary exposure from the permitted food contact uses (above) and ensuring that the cumulative dietary exposure from all uses is supported by the available toxicological information.

Dietary exposure estimates, expressed as dietary concentrations (DC) or estimated daily intakes (EDIs), typically rely on combining migrant concentrations in food (or food simulants) with information on use of food contact articles that might contain the substance. This is typically accomplished by using packaging factors, which include consumption factors (CF) and food distribution factors (f_Ts) as tabulated in our Chemistry Guidance, Appendix IV (US FDA, 2007). The expression relating migrant levels in food and packaging factors to DC for the purpose of estimating exposure for single-use articles is:

$$DC = CF \times < M \geq CF \times [(M_{aq})(f_{aq}) + (M_{ac})(f_{ac}) + (M_{al})(f_{al}) + (M_{fat})(M_{fat})]$$

$$EDI = DC \times 3 \text{ kg food/person/day}$$

Cumulative exposure estimates, expressed as cumulative EDI (CEDI) or a cumulative DC (CDC), are the sum of the exposure estimates from the permitted uses. It is this value that is crucial in determining the overall safety of the substance in question.

Safety testing recommendations for exposure tiers are discussed in our Toxicology guidanceGuidance (US FDA, 2002). At CDCs greater than 50 ppb (or 2.5 μg/kg/d), the potential toxicity of an FCS should be evaluated by two subchronic oral toxicity tests, one in rodent species and one in a non-rodent species. These studies should provide an adequate basis for determining a no-observed effect level (NOEL) or no-observed adverse effect level (NOAEL) and whether additional studies should be conducted.

The NOEL or NOAEL derived from the critical study or studies identified in the safety assessment is used to calculate a margin of exposure (MOE). The MOE is the ratio between the estimated CEDI and the NOEL or NOAEL. To adequately ensure safety of the food contact substance (FCS), the MOE should exceed the margin of safety (MOS), which is the combined value of all relevant and appropriate safety or uncertainty factors used to describe the toxicological data. More detailed discussions on the safety assessment are available elsewhere (Bailey et al., 2008; Twaroski et al., 2007).

3. Methods

3.1. Selection of chemistry studies

With regard to information in Agency files, the Food Additive Petitions (FAP) that resulted in regulation listings in 21 CFR 170–199, in addition to the effective FCN submission, were identified, with the submissions grouped by the applicable regulations or uses, with consideration given to the previous DC contributions and the CDC (Table 1). The pertinent conclusions on migration to food and exposure in each submission were summarized and updated, as necessary, to reflect the current science and regulatory approaches used by FDA. For example, in most cases it was necessary to recalculate <M> values using new and/or updated packaging factors.

A literature search was also conducted using Web of Science (Thomson Reuters) with the search terms "Irganox 1076" and the CAS Registry No. (CASRN), with specific emphasis on recent publications describing I-76 loading levels in commercial food packaging, or I-76 migration to food or food simulants. This was done to identify recent migration levels in food that may be useful in updating consumer exposure. We were not able to identify publications providing a comprehensive list of I-76 migration values into food or food simulants.

3.2. Selection of toxicology studies

A general safety assessment was performed for this postmarket review and aimed to consider all relevant toxicological studies. Therefore, all studies in OFAS archival records on I-76 were evaluated for inclusion in the safety assessment. These studies included 4 genetic toxicity studies, 3 subchronic toxicity studies, 2 chronic toxicity or carcinogenicity studies, and 3 reproductive or developmental toxicity studies. For a study to be included in the safety assessment, the study needed to contain adequate assessment parameters, contain sufficient raw data for analysis, and be generally compliant with standardized and validated protocols (*i.e.*, FDA Redbook, OECD Test Protocols, etc). Four studies were identified that provided supplemental information but were not considered critical to the safety assessment. These studies were of short duration (4 week or less) or provided information in a limited context; for example, data on the elimination of I-76 in the rat.

A search of the public scientific literature was performed using keywords "Irganox 1076," "Irganox," wildcard "toxic∗," and the CASRN for any relevant information not captured by search of the OFAS archived records. No studies in the public literature were identified regarding the safety or toxicology of I-76 that were relevant to the present assessment, with the exception of a single study performed using an antioxidant similar, but not identical, to I-76 (Lake et al., 1980).