Updated Safety Assessment of Tris(2,4-di-tert-butylphenyl) Phosphite (Irgafos 168) Used in Food Contact Applications

Laura C. Markley, Adejoke Ogungbesan, Andreś Gonzalez-Bonet, Omari J. Bandele, Allan B. Bailey, Geoffrey W. Patton

Division of Food Contact Substances, Office of Food Additive Safety, Center for Food Safety and Applied Nutrition, U.S. FDA, College Park, MD

Highlights

Antioxidants, like Irgafos 168, are added to plastic food contact articles to reduce degradation of the polymer.

Our work determined there is no safety concern, in general, for the current authorized uses of Irgafos 168 in food contact articles nor a safety concern for neurotoxicity.

Background

- Polymers undergo thermal degradation during processing and long-term use, which may result in undesirable changes to the polymer.
- Primary and secondary antioxidants (AO) are often added to stabilize polymers during thermal processing and the long-term use of the food contact article.

Primary AOs contain reactive amino (R_2-NH) or hydroxyl (R-OH) groups that can donate hydrogen (H·) to peroxyl radicals (p-ROO·) to form hydroperoxides (p-ROOH) and prevent the abstraction of hydrogen from the polymer backbone.

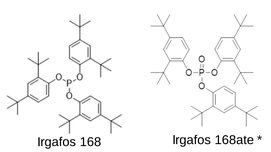
ROH + p-ROO· → RO· + p-ROOH

Secondary AOs react with (p-ROOH) to form inert products preventing creation of reactive oxygen radical (p-RO·) and hydroxyl radical (·OH).

$(RO)_3P$ + p-ROOH → $(RO)_3P{=}O$ + p-ROH

The combined protective effect of primary and secondary AO use is often much greater than can be achieved with either alone.

- During the use of polymer AOs in food applications, by their very nature, degradation products are formed that may migrate to food.
- Commonly used secondary AOs in the production of polymers are trivalent phosphorous compounds, such as Irgafos 168 (structure shown in **Figure 1**).



Irgafos 168

Irgafos 168ate *

Figure 1. Chemical Structure of Irgafos 168 (CASRN 31570-04-4) and Irgafos 168ate (CASRN 95906-11-9)

* Irgafos 168ate refers to the phosphate form of Irgafos 168

- The putative toxicological concern for Irgafos 168 is the potential for the phosphate degradation species, Irgafos 168ate, to present a hazard for neurotoxicity similar to some other organophosphates.

- **<u>Purpose of our analysis</u>: To evaluate the dietary exposure and oral toxicity data of Irgafos 168 (and Irgafos 168ate) when used as a secondary antioxidant in food contact applications.**

Methods

Exposure Assessment Methods

- Performed an extensive review of the U.S. food-contact regulatory history for the use of Irgafos 168 (**Figure 2**)

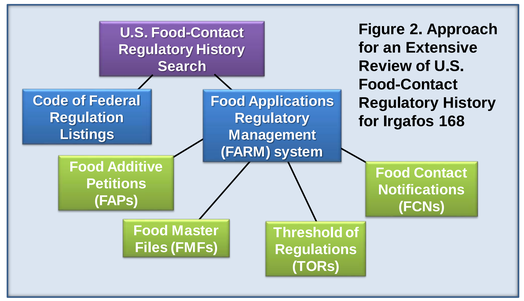


Figure 2. Approach for an Extensive Review of U.S. Food-Contact Regulatory History for Irgafos 168

- Determined range of applications for the use of Irgafos 168 in food-contact polymers
- Predicted degradation scheme for Irgafos 168 through literature search
- Derived a combined cumulative estimated daily intake (CEDI) for Irgafos 168 (and Irgafos 168ate) (FDA 2007)

Safety Assessment Methods

- Searched various databases (FARM, CERES, Appian-TEMPO, ChemIDPlus, Pubmed/PubChem, SciFinder, Google, ECHA, EPA Comptox Dashboard, IARC, NTP, Toxtree, Web of Science) using CASRN and/or name(s) of Irgafos 168 and Irgafos 168ate
- For the neurotoxicity assessment, we investigated the potential reactivity of Irgafos 168ate with the serine residue in the acetylcholinesterase (AChE) active site and subsequent inhibition of AChE.
- Determined an acceptable daily intake (ADI) value based on a point of departure (POD) from the critical animal toxicity study and a safety factor (SF) value (**Figure 3**) (FDA 2002)

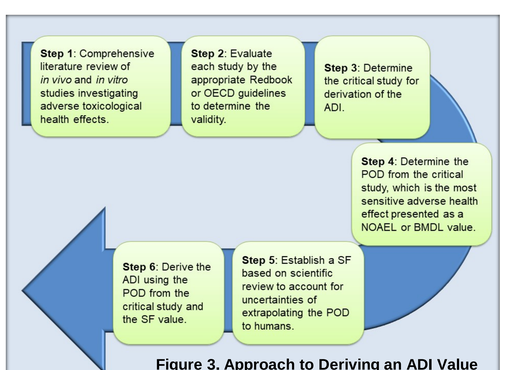


Figure 3. Approach to Deriving an ADI Value

Results

Exposure Assessment Results

- U.S. food-contact regulatory history use of Irgafos 168-containing polymers in food contact applications concluded:
  - I-168 and I-168ate migrate into aqueous foods at much lower concentrations than in fatty foods.
  - I-168 migrated into food at similar concentrations whether by microwave heating (≤950 W, 1 h at 80°C) or thermal heating (1 h at 80°C).
- Range of applications for use of Irgafos 168 in food-contact polymers were:
  - Used synergistically with primary AOs including in polyolefins, polycarbonates, polyamides, polyesters, styrenics, adhesives, natural and synthetic tackifier resins, elastomers, and other organic substrates
- Predicted degradation scheme for Irgafos 168 (**Figure 4**):
  - Combination of oxidation and hydrolysis steps with Irgafos 168ate being the most common degradation pathways (**#2, Figure 4**)
- Calculation of the combined CEDI of Irgafos 168 and Irgafos 168ate:
  - Determined to be 0.09 mg/kg bw/day (or a cumulative dietary concentration (CDC) of 1.8 ppm for a 60 kg person).

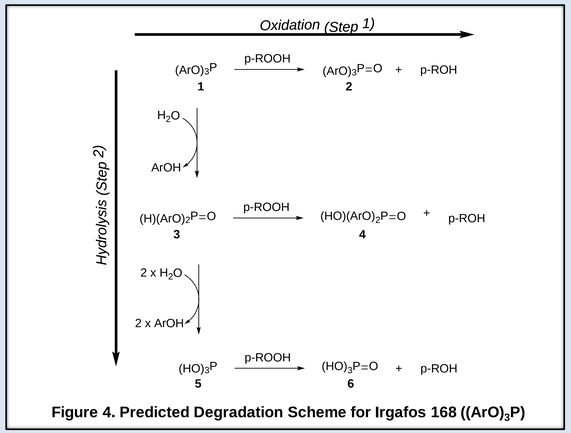


Figure 4. Predicted Degradation Scheme for Irgafos 168 ($(ArO)_3P$)

Safety Assessment Results

- Comprehensive literature search concluded:
  - Irgafos 168ate was no more toxic than Irgafos 168
  - Potential concerns for neurotoxicity of Irgafos 168ate were diminished by a hen study that was concluded to be negative for neurotoxicity (CIBA-Geigy 1978, CIBA-Geigy 1980).
- Structure Activity Relationship (SAR) Analysis of the reactivity of Irgafos 168ate with AChE concluded:
  - Expected reduced rate of reactivity due to three bulky aryl substituents (i.e., 2,4-DTBP) that would slow the reaction rate with AChE (an SN2 reaction that is known to be sensitive to steric effects) reducing concern of the potential neurotoxicity of Irgafos 168ate
- Critical toxicity study and POD from the evaluation of several oral animal toxicity studies was determined to be:
  - Two-year (dietary) combined chronic toxicity/ carcinogenicity study in rats administered Irgafos 168 for 105 weeks at dose levels of 0, 250, 750, or 2,000 ppm (LSR 1985).
  - POD was the no-observed effect level (NOEL) of 2,000 ppm (or 100 mg/kg bw/day) based on no treatment-related effects.
- Appropriate SF to extrapolate the POD to humans was:
  - 10 for intraspecies variability (SF_1), 10 for interspecies variability (SF_2), and 1 for data quality including length of study and reproduced effect seen in multiple species (SF_3)
- Derived an ADI for Irgafos 168 of 1 mg/kg bw/day by the following calculation:

$$\text{ADI} = \frac{\text{POD}}{(SF_1 \cdot SF_2 \cdot SF_3 = SF)} = \frac{100\ \text{mg/kg bw/day}}{(10 \cdot 10 \cdot 1) = 100} = 1\ \text{mg/kg bw/day}$$

- For Irgafos 168 and its degradation products, the combined CEDI (0.09 mg/kg bw/day) is below the ADI (1 mg/kg bw/day).
- There are no safety concerns for the use of Irgafos 168 as a secondary antioxidant at the current use levels, and no evidence to suggest that the degradation products pose a risk for neurotoxicity.

Conclusions

- U.S. FDA performed a post-market review of the food contact use of Irgafos 168.
- For Irgafos 168 and its degradation products, the combined CEDI (0.09 mg/kg bw/day) is below the ADI (1 mg/kg bw/day).
- Therefore, there is no safety concern for Irgafos 168 based on the current authorized uses, and the degradants of Irgafos 168 do not appear to pose a safety concern for neurotoxicity.

Acknowledgements

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