Radiation Physics and Chemistry
Volume 103, October 2014, Pages 188-193

Review

A critical review on toxicological safety of 2-alkylcyclobutanones

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https://doi.org/10.1016/j.radphyschem.2014.05.065
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Highlights

- Mutagenicity 2-ACBs on the microorganisms was not observed.
- Several *in vitro* studies demonstrated the cytotoxicity of 2-ACBs.
- Genotoxicity of 2-ACBs was suggested, but elucidation of the mechanism is needed.
- 2-dDCB was metabolized into cyclic alcohol and excreted in feces.
- Further studies for toxicity of 2-ACBs following international guidelines are needed.

Abstract

2-Alkylcyclobutanones (2-ACBs) are known as unique radiolytic products generated from the major fatty acids and triglycerides in food through only irradiation. Since 1990, studies on the toxicological safety of 2-ACBs have been conducted extensively with synthetic compounds. Mutagenicity tests of 2-ACBs on the microorganisms reviewed in this study clearly indicate that no evidence was observed, while several *in vitro* studies demonstrated the cytotoxicity of 2-ACBs through cell death. Moreover, the genotoxicity of 2-ACBs was suggested as DNA strand breaks were observed. However, these findings should be interpreted with caution because genotoxicity may result from cytotoxicity, which causes DNA damage or from cell membrane destruction and indirect oxidative DNA damage. Therefore, elucidation of the mechanism of genotoxic effects is needed. With regards to the suggestion of Raul et al. (2002) who showed the promoting effect of colon cancer by the administration of 2-ACBs, further studies are needed to correct some experimental design errors. Moreover, an *in-vivo* experiment that evaluated the metabolism of 2-ACBs has revealed that 2-dDCB was metabolized into cyclic alcohol and excreted through fecal discharge. In conclusion, it is considered that the ingestion of 2-ACBs through irradiated foods is unlikely to affect the human health. However, more specific studies are required to identify the fate of 2-ACBs in body and the LD_{50} values. The determination of chronic toxicity by long-term exposure to low concentrations of 2-ACBs has to be evaluated more clearly to determine if these compounds are safe to human.

Introduction

Food irradiation is a physical treatment in which food commodities are exposed to a defined dose of ionizing radiations such as gamma rays, electron beams, and X-rays in order to control foodborne pathogens, reduce the microbial load and insect infestation, inhibit the germination of root crops, and extend the durable life of perishable products (Farkas, 2006). Since the 1980s, radiation technology has been studied extensively and has been used increasingly as an effective method to improve the hygiene of food and public health products (Kunstadt et al., 1993). Irradiation technology is currently being used on more than 60 food types in more than 40 countries worldwide (Arvanitoyannis, 2010).

Food irradiation is perhaps the most studied food processing technology for toxicological safety in the history of food preservation. The wholesomeness of irradiated food has been carefully evaluated by an unprecedented width of research and testing for more than 50 years. At an international level, the need to consider the wholesomeness of irradiated foods was emphasized at a meeting sponsored by FAO, IAEA, and WHO in Brussels in 1961. The appropriate studies required to ascertain the wholesomeness were discussed by a Joint FAO/IAEA/WHO Expert Committee on Food Irradiation (JECFI) in Rome in 1964. Taking as a premise that the irradiation of food resulted in the production of radiolytic products in the foods, the Committee adopted the view that these products represented additions to the food. It therefore concluded that the establishment of the safety of irradiated foods should follow procedures similar to those generally used for evaluating the safety of food additives and should be pursued on a food-by-food basis (WHO, 1966).

A subsequent meeting was convened to assess the wholesomeness of irradiated wheat, potatoes, and onions in Geneva in 1969. The next Joint Expert Committee, convened in 1976, reviewed a large number of animal studies on various irradiated foods. The committee also reviewed the results of radiation chemistry studies on the major components of food; it noted that many of the radiolytic products identified were present in food treated by heat and other processes and considered that the health hazard from the concentrations found in irradiated foods was probably negligible (WHO, 1977).

In 1980, the JECFI had reviewed numerous microbiological, nutritional, and toxicological studies of irradiated foods and concluded that " the irradiation of any food commodity up to an overall average dose of 10 kGy presents no toxicological hazard and introduces no special nutritional or microbiological problems" (WHO, 1981). In the report, however, 2-alkylcyclobutanones (2-ACBs) were not reviewed by the committee. Several studies on identification of the radiolytic products such as hydrocarbons and volatile compounds in irradiated beef, ham, chicken, and starches were just reviewed.

Since 1990, studies on the toxicological safety of 2-ACBs have been conducted extensively with synthetic compounds because a high dose of pure 2-ACBs could be applied to cells or rodents. In 1998, Delincée and Pool-Zobel (1998) reported that synthetic 2-dodecylcyclobutanone (2-dDCB), a type of 2-ACBs created from the irradiation of palmitic acid in fat, possibly causes genotoxicity. Additionally, 2-tetradecylcyclobutanone (2-tDCB) has been shown to promote colon cancer (Raul et al., 2002). The discrepancies between these results and the reports from the JECFI have initiated debates between academia and consumer groups regarding the safety of food irradiation.

Therefore, the aim of this review is to examine the safety of 2-ACBs, to suggest future studies examining 2-ACBs, and to provide a foundation for understanding the safety of irradiated foods.

Section snippets

Characteristics of 2-ACBs

Ionization induces the production of highly active free radicals and chemical changes. When fat in food are irradiated, the disrupted fatty acids form 2-ACBs, which are cyclic compounds containing four carbon rings (Fig. 1). 2-ACBs have the same number of carbons as the precursor fatty acid, and an n-4 alkyl group side chain, which is formed by electron loss of the oxygen molecule in the fatty acid/triglyceride carbonyl group through ionization and consecutive rearrangement, is linked to the…

in vitro toxicity studies

in vitro toxicity studies conducted from 1998 through 2013 are provided in Table 1. Delincée and Pool-Zobel (1998) studied the influence of 2-dDCB on rat and human colon cells. Using a comet assay, these researchers revealed that 2-dDCB (0.3–1.25 mg/mL) induced DNA strand breaks and that 2-dDCB (1.25 mg/mL) was cytotoxic in approximately 80% of human colonic cells. Subsequently, Delincée et al. (2002) treated human colon tumor cell lines (HT29 and HT29 clone 19A) with 2-tDCB (6–100 μg/mL) for 30…

Discussions

Although the above *in vitro* and *in vivo* experiments clearly indicate 2-ACB-induced cytotoxicity through cell death, 2-ACB-induced genotoxicity based on evaluation data such as DNA damage through the comet assay should be carefully evaluated. Specifically, genotoxicity may result from cytotoxicity, which causes DNA damage or result from cell membrane destruction and indirect oxidative DNA damage. However, the mechanism has not yet been elucidated. In one unique *in vivo* toxicity experiments…

Acknowledgments

This research project was co-supported by the Basic Research Support Program of Korea Atomic Energy Research Institute and the National Nuclear Research & Development Program of the Korea Science and Engineering Foundation grant funded by the Korean Government….

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Food Chem. (2012)

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2022, Life Sciences in Space Research

Citation Excerpt :

…After irradiation, the FA moieties in the triacylglycerols are affected and lead to the formation of 2-alkylcyclobutanones which are not naturally present in food systems and thus are good indicators of radiation exposure on FAs in food (D'Oca and Bartolotta, 2018). As an example, figure 4 shows the radiolysis of palmitic acid (C16:0 FA) leading to the formation of 2-dodecylclobutanne (2-DCB), which is a unique marker for this process on C16:0 FA, and can also be analysed by gas chromatography-mass spectrometry (GC-MS, D'Oca and Bartolotta, 2018; Song et al., 2014). In the case of proteins, phenylalanine widely exists within food products (Miyahara et al., 2002).…

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Wholesomeness and safety aspects of irradiated foods

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…These studies have reported that 2-ACBs exhibit no mutagenic or genotoxic effects on mammalian cell lines at low concentrations. However, the consumption of these chemicals at higher doses has resulted in cytotoxicity and damage to the genetic material in rat and human colon cells (Song et al., 2014). More encouragingly, irradiation can control the formation of nitrosamine and nitrite-related products in cured meat.…

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Determination of 2-alkylcyclobutanones in ultraviolet light-irradiated fatty acids, triglycerides, corn oil, and pork samples: Identifying a new source of 2-alkylcyclobutanones

2017, Food Chemistry

Citation Excerpt :

…2-Alkylcyclobutanones, 2-ACBs, are among the products formed when fatty acids and triglycerides in lipid-containing foods are exposed to ionizing radiation (Fig. 1) (Horvatovich, Miesch, Hasselmann, Delincée, & Marchioni, 2005; Nawar, Zhu, & Yoo, 1990). There is accumulated evidence to suggest that only ionizing radiation alone, including gamma-radiation, X-rays, or accelerated electron beams could generate 2-ACBs in food; but other food preservation/cooking methods such as UV-irradiation, microwave/oven heating, steaming and roasting do not generate such molecules (Crews, Driffield, & Thomas, 2012; Driffield et al., 2014; Ndiaye, Jamet, Miesch, Hasselmann, & Marchioni, 1999; Song et al., 2014). Therefore, 2-ACBs are considered as unique radiolytic products and have been used as marker molecules for identifying lipid-containing foods that have been treated with ionizing radiation (Chan, Ye, & Leung, 2014; Horvatovich, Miesch, Hasselmann, & Marchioni, 2000; Stevenson & Crone, 1990).…

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Rapid determination method for 2-DCB in irradiated pork by ASE–Al<inf>2</inf>O<inf>3</inf>–GC–MS

2017, Radiation Physics and Chemistry

Citation Excerpt :

…In our study, 2-DCB concentrations were expressed on a sample weight basis; therefore, the level of 2-DCB was relatively lower than that on a fat basis. The chronic toxicity of 2-ACBs has recently aroused concern according to reported literature (Song et al., 2014). Therefore, a sample weight basis for expressing 2-DCB concentrations would be meaningful to evaluate the risk of these compounds exposed to human body when irradiated food was selected as a diet.…

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