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WHO Statement on 2-Dodecylcyclobutanone and Related Compounds

In 1972 small amounts of 2-dodecylcyclobutanone (2-DCB) were reported to be formed in irradiated triglycerides (fats). In 1990 the compound was first isolated in chicken irradiated at high doses and was subsequently studied as a possible marker for identifying certain irradiated food. 2-DCB and related compounds could presumably be formed at detectable levels when foods containing high levels of fat were irradiated. Generally, however, 2-DCB is expected to be produced at very low levels in food processed with low to moderate dose of irradiation, as reflected in a *G*-value of 0.001. Though stable in the irradiated chicken stored at room temperature, some decomposition occurs with exposure to heat, light, and oxygen. Therefore, the levels of 2-DCB in food as consumed would likely be lower than that measured in raw food. 2-DCB.

Aware of the possible low level presence of 2-DCB and related cyclobutanones in certain irradiated food, the 1997 FAO/IAEA/WHO Study Group[1] considered that the safety for consumption of irradiated food containing 2-DCB had been demonstrated on the basis of studies conducted by the Raltech Laboratory in the early 1970's on chicken irradiated at high doses, which included chronic feeding studies, teratology studies and a series of in vitro tests. Based on chemical analyses made subsequent to the Raltech studies, the level of 2-DCB in chicken irradiated at 59 kGy while frozen at -30°C would have been about 1.7 µg of 2-DCB per g of chicken (fresh weight). These studies, which involved dogs and mice as well as bacterial and mammalian cell *in vitro* genotoxicity tests, showed no evidence of any adverse effects attributable to the irradiation and, therefore, to 2-DCB and other cyclobutanones. Within the limits of sensitivity of such studies, it can be confirmed with reasonable certainty that any hazard, if present, is very low or negligible.

The Study Group was also aware that a preliminary report of recent studies had raised new concerns about the safety of 2-DCB, but the Study Group questioned the reliability of the studies because of several apparent experimental deficiencies. One serious problem was that the chemically synthesized sample of 2-DCB was handled under conditions that may have promoted its decomposition, and the actual identity of the compound used was not verified before the tests were conducted. Another major problem was the exclusive use of the *comet assay*, which tends to give false positive findings of genotoxicity for tested substances, including vitamin C. Most experts in the field of genotoxicity testing do not believe that the comet assay has been sufficiently validated and most national regulatory authorities do not accept the *comet assay* as a basis for assessing genotoxicity at this time.

One author of the studies has acknowledged that based on the limitations of the studies, it would be premature to draw the conclusion that 2-alkylcyclobutanones are a health hazard. Subsequently in 2001, the studies were repeated with purified 2-alkylcyclobutanones but still used the questionable *comet assay* as well as other unvalidated tests, but did include the widely recognized Ames test. While lack of mutagenic activity of these compounds was confirmed in the Ames test, certain findings with the unvalidated tests suggested a potential for 2-alylcyclobutanones to cause cancer. However, the authors cautioned that the relevance of the findings to the human exposure situation needed to be carefully considered. In July 2002 the European Commission's Scientific Committee for Food addressed this issue and dismissed these studies as not being relevant for assessing the safety of irradiated food[2]. The Committee pointed to the numerous long-term feeding studies in animals, already cited by WHO experts, which, they said, provide reassurance as to the safety of fat-containing irradiated foods.

In a recent published report, the metabolism of 2-alkylcyclobutanones was studied in animals[3]. Rats were fed about 1 mg of 2-tetradecyl- or 2-tetradecenyl-cyclobutanone in drinking water each day for 4 months. At the end of 4 months, body weight gain values were similar for the treated rats and for control rats fed the standard diet. Although 2-alkylcyclobutanones are fat soluble substances, only a very small amount of the ingested dose appeared in adipose tissue. This was estimated to be 0.002 - 0.008% of the total ingested dose. In addition, only small amounts (0.1 - 0.3% of the total ingested dose) were detected in fecal matter. This study provides evidence that these compounds do not accumulate in adipose tissue, but are rapidly metabolized and/or degraded in animals.

Therefore, based on the current scientific evidence, including the long-term feeding studies, 2-DCB and 2-alkylcyclobutanones in general do not appear to pose a health risk to consumers. Consequently, at this time, WHO has no basis to question the conclusions of several joint FAO/IAEA/WHO expert groups as well as the scientific opinion of many national and regional expert advisory bodies that irradiated foods are safe and nutritionally adequate. WHO continues to encourage further research to be conducted in accordance with scientifically accepted protocols for assessing food safety to help resolve any remaining uncertainties about the toxicity/carcinogencity of these compounds. In this regard, WHO reiterates its previously stated[4] willingness to re-open the risk assessment of irradiated foods if new evidence indicates a potential public health risk.

[1] WHO, High-dose Irradiation: Wholesomeness of Food Irradiated with Doses Above 10 kGy, Report of a joint FAO/IAEA/WHO Study Group, WHO Technical Report Series 890, Geneva, 1999

[2] European Commission, Statement of the Scientific Committee on Food on a Report on 2-alkylcyclobutanone (expressed on 3 July 2002), SCF/CS/NF/IRR/26 ADD 3 Final

[3] Horvatovich, P., et al, Detection of 2-Alkylcyclobutanones, Markers for Irradiated Foods, in Adipose Tissues of Animals Fed with These Substances, Journal of Food Protection, 64:10 (2002)

[4] Joint FAO/WHO Food Standards Programme, Statement of the WHO Representative to the Codex Committee on Food Additives and Contaminants, ALINORM 03/12, para 79, Rome, 2002