CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

World Health Organization

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON CONTAMINANTS IN FOODS

17th Session
15-19 April 2024
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DISCUSSION PAPER ON ACRYLAMIDE IN FOODS

(Prepared by India and co-chaired by Saudi Arabia)

INTRODUCTION

1. At the 16th session[1] of the Codex Committee on Contaminants in Foods (CCCF) agreed to establish an EWG, chaired by India and co-chaired by Saudi Arabia, to prepare the discussion paper on Acrylamide (AA) in foods to look into the effectiveness and feasibility of risk management measure(s) for consideration by CCCF17.

2. The purpose of this discussion paper is to summarize information on the health risks, toxicology, analysis, and knowledge gaps related to the presence of acrylamide in foods. The discussion document mainly focuses upon the most recent evaluations of Joint FAO/WHO Expert Committee on Food Additives (JECFA) in its 64th (2005)[2] and 72nd (2010)[3] meetings and reports from other member countries and organizations on risk management measures.

3. AA was propelled into the spotlight in 2002 when the Swedish National Food Administration and the University of Stockholm reported considerably high levels of this probably carcinogenic compound in commonly consumed foods such as bread, coffee, potato crisps, French fries and many others.[4] [

FORMATION IN FOOD

4. AA formation starts with the reaction of a carbonyl compound (a reducing sugar) with the amino acid asparagine, resulting in the corresponding N-glycosyl conjugation and the formation of Schiff base (after dehydration at high temperature). After its decarboxylation, the Schiff base may lead directly to AA and an imine or followed by hydrolysis to aminopropionamide and carbonyl compounds. Further, aminopropionamide may also yield AA after the elimination of an ammonia group (Figure 1).

5. AA is formed mainly from free asparagine and reducing sugars during high-temperature cooking and processing of common foods, principally through Maillard reactions. Given its toxic effect on humans and animals, the last 20 years have seen an increased interest in research devoted to the AA. Large concentrations of AA can be found in popular staples such as coffee, bread or potato products (Annexure I).

6. The Maillard reaction, in the presence of asparagine, has been shown to be the main pathway for AA formation in a wide range of foods processed at high temperatures.[5]

7. AA is mainly formed during heat processing (>120 °C) of foods – primarily those derived from plant origin such as potato and cereal products. Stable isotope-labelled experiments have shown that the backbone of the AA molecule originates from the amino acid asparagine. Asparagine alone could in principle form AA by direct decarboxylation and deamination, but the reaction is inefficient, with extremely low yields. However, asparagine in the presence of reducing sugars (a hydroxycarbonyl or reactive dicarbonyls) furnishes AA in the range up to 1 mol % in model systems.

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[1] REP23/CF16, para 133 (iv)

[2] Joint Expert Committee on Food Additives (JECFA). Summary and Conclusions: Sixty-fourth meeting, Rome, 8-17 February 2005.

[3] Joint Expert Committee on Food Additives (JECFA). Summary and Conclusions: Seventy Second meeting, Rome, 16-25 February 2010

[4] Swedish National Food Administration. Analytical methodology and survey results for acrylamide in foods. http://www.slv.se/engdefault.asp. 2002.

[5] CX/FAC 06/38/35, Discussion paper on Acrylamide

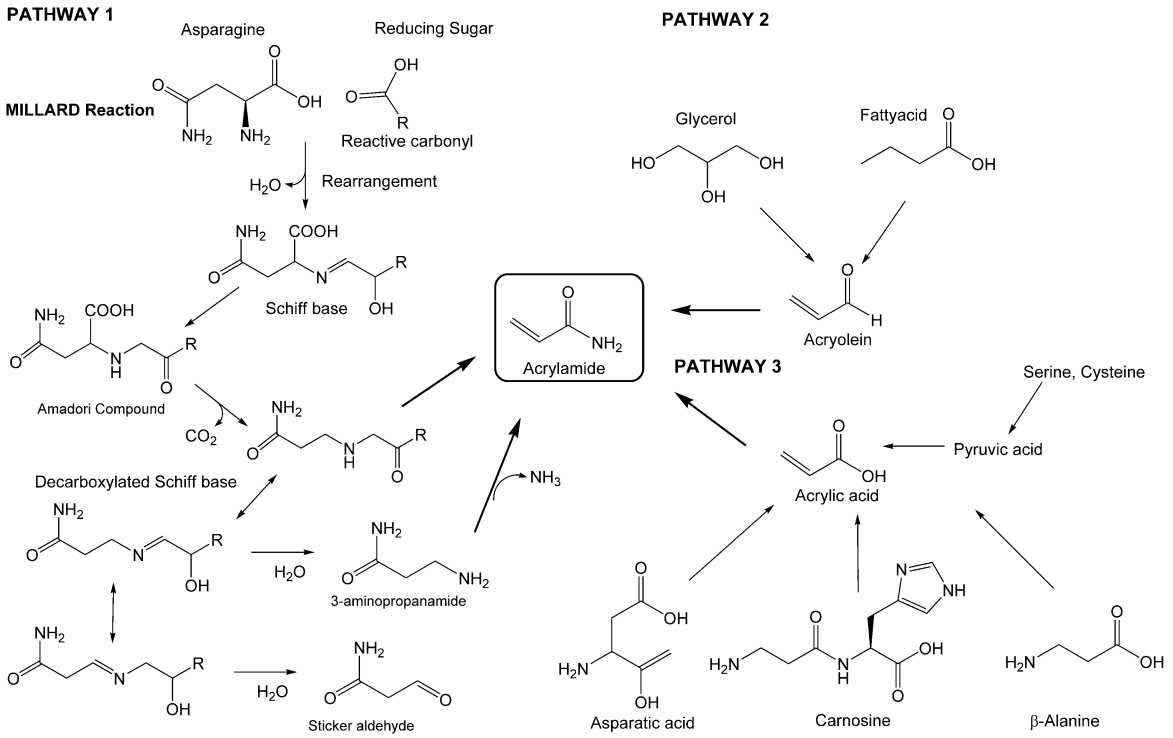

Figure 1: Proposed pathways for formation of Acrylamide in Foods.

8. On the other hand, non-asparagine routes (alternative pathways) leading to AA have been published over the past years.[5] However, these non-asparagine pathways may be considered as of marginal importance because studies in potato- and cereal-based foods have demonstrated the importance of asparagine by effectively reducing AA through the use of the substrate-selective enzyme asparaginase.

TOXICOLOGY AND EPIDEMIOLOGY

TOXICOKINETICS

9. AA is rapidly absorbed from the gastrointestinal tract after consumption and widely distributed to the tissue. Ingested AA is taken up into the circulation and excreted mainly in the urine as mercapturic acid conjugates (i.e metabolites of AA and glycidamide). [2,3,5-6]

10. The majority of AA is conjugated with glutathione and small amount is activated by the cytochrome P-450 (CYP2E1) enzyme to a reactive epoxy compound, glycidamide (GA). GA is further metabolized and detoxified by glutathione.[6]

11. Studies on rats, mice and humans suggest efficient human metabolism of AA to glycidamide. However, in humans there is considerable variability in the extent of AA conversion to glycidamide, which appears to be related to the inter-individual variability in the amount of liver CYP2E1.

12. Experiments in rats, mice, dogs, and pigs have shown that the AA is rapidly distributed to all tissues including the testes, and after passing the placental barrier AA reaches the foetus as well. The Hb adduct carbamoyl-ethyl-valine was measured to give an orientation on internal exposure levels. As such the adduct provides a bridge to endpoints of potential toxicity.[6-9]

[6] World Health Organization. Health Implications of Acrylamide in Food. **Error! Hyperlink reference not valid.**.
[7] WHO Technical report series, Evaluation of Contaminants of Foods, Seventy Second report of the Joint FAO/WHO Expert committee on Food additives https://www.who.int/publications/i/item/9789241209595
[8] WHO FOOD ADDITIVES SERIES: 63, FAO JECFA MONOGRAPHS Safety evaluation of certain contaminants in food (Acrylamide Addendum pg 1-151)
[9] European Union Scientific Committee on Food. Opinion of the EU Scientific Committee on Food on new findings regarding the presence of acrylamide in food, July 3, 2002.

TOXICODYNAMICS

13. The main toxic endpoints of AA are neurotoxicity in humans and animals, developmental and reproductive toxicity in rodents, and genotoxicity and carcinogenicity in rodents.[10-12]

14. Neurotoxicity of AA has been reported due to accidental intoxications and from chronic occupational exposures. Although primarily peripheral neuropathies were reported other parts of the nervous system are also affected, like cerebellar Purkinje cell damage and degradation of distal axons in the central nervous system and peripheral nervous system.[8]

15. Moreover, degradation of terminal nerves has been reported to lead to impairment of cognitive functions and damage to the cerebral cortex, thalamus and hippocampus. While considering mean and high dietary consumption as 0.001 mg/kg/bw/day and 0.004 mg/kg/bw/day there were no adverse neurological effects but have morphological changes in nerves.[3,7,8]

ANALYTICAL METHODS

16. When the occurrence of AA in food was discovered in Sweden in 2002 a liquid chromatographic– tandem mass spectrometric (LC-MS/MS) method for its quantification was introduced. The method involves extraction with water and clean-up using solid-phase extraction (SPE) and further characterizing the parent and daughter ions of AA.[13]

17. Chromatographic methods enable fast, accurate and reproducible determination of AA. The most widely used methods are based on the LC-MS-MS or gas chromatography–mass spectrometry (GC-MS).

18. Determination of AA using LC-MS/MS may avoid derivatization and has the advantage of rather high sensitivity and stability. Using ultra performance liquid chromatography (UPLC)-MS/MS or UPLC– time of flight (TOF)-MS may further reduce the sample analyses and labour time and achieve limit of quantification of < 1 ug/kg^{-1}.

19. GC-MS after bromination is the best GC approach so far, because this method is a relatively mature coupled technique with adequate sensitivity and multiple ion monitoring. Application of GC-MS/MS or coupling to high-resolution MS would lower the detection limit of certain foods even further to 1–2 μg kg^{-1}.

20. An inter-laboratory study on the LC-MS/MS and the GC-MS methods for the quantification of AA in bakery and potato products in the 20–9000 μg kg^{-1} range found the performance of the HPLC-MS-MS method to be superior to that of GC-MS.[14]

21. Besides MS detection methods HPLC–diode-array detection (DAD), HPLC-UV detection, GC–electron capture detection (ECD), capillary zone electrophoresis (CZE) immuno-enzymatic tests and, recently, electrochemical biosensors have been introduced. Immuno-enzymatic tests are based on the selective binding of antigens to be quantified by antibodies. The electrophoretic techniques require short time of analysis and have a high-resolution power.[13]

22. Near-infrared spectrometry (NIR) and computer vision-based image analysis broaden the method selection for the analysis of AA or for controlling AA levels in food production. Since several studies reported a good linear relationship between browning and AA accumulation in chips and in model systems image analysis of browning may act as an indirect measure of AA concentration as an online process control tool for the frying and baking industry.

23. The EC Joint Research Centre's (JRC) task force along with German Institute for Materials Research and Testing, has developed certified reference materials for acrylamide for environment and food beverage purposes as part of HEATOX Project.[15]

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[10] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Acrylamide. [60], 389-433. 1994. Lyon, France, International Agency for Research on Cancer.

[11] National Toxicology Program. NTP-CERHR expert panel report on the reproductive and developmental toxicity of acrylamide. http://cerhr.niehs.nih.gov/news/acrylamide/final_report.pdf.

[12] Scientific Opinion on acrylamide in food, EFSA Panel on Contaminants in the Food Chain (CONTAM), EFSA Journal 2015;13(6):4104

[13] Wenzl,T., De La Calle,M.B., & Anklam,E. Analytical methods for the determination of acrylamide in food products: a review. Food Addit. Contam. 20, 885-902 (2003).

[14] Wenzl,T. et al. Evaluation of the results from an inter-laboratory comparison study of the determination of acrylamide in crispbread and butter cookies. Anal. Bioanal. Chem. 379, 449-457 (2004).

[15] HEATOX (Heat generated food toxicants: identification, characterization, and risk minimization): EC Project FOOD_CT-2003-506820-STREP. www.heatox.org. 2003.

OCCURENCE DATA

24. The level of acrylamide in foods varies depending on many factors such as the type and content of food, processing technique employed, and storage conditions.

25. JECFA has earlier comprehensive analysis of occurrence data of 24 countries to assess the major contributing foods and full extent of acrylamide in diet was unclear.[5,16]

26. In this context, much research, including traditional foods specific to societies, especially foods that are widely consumed around the world, has been carried out till 2008 and does not necessarily indicate covering all the commodities of countries (Annexure 1, Table 1).

27. WHO GEMS data indicate no acrylamide in fruits, chicken meat, coffee beans and herbal tea. Whereas high levels of acrylamide is reported for snack foods 1286.8 ug/kg, potatoes-based snacks 1583.7 ug/kg and coffee beverage as 245 ug/kg.

28. Recent studies indicated acrylamide levels as 779–1299 µg/kg in French fries, and 211–3515 µg/kg in potato chips, which is quite high compared to the acrylamide levels in other foods.[12] This warrants a need for evaluation of occurrence data of several commodities and traditional foods.

29. Acrylamide levels have been reported to be 31–454 µg/kg in the bread, 135–1139 µg/kg in coffee, and 5.30–79.5 µg/kg in ready-to-drink (brewed) coffee.[12]

DIETARY EXPOSURE

30. The JIFSAN 2004 Acrylamide in Food Workshop Working Group, which focused on exposure and biomarkers, examined various epidemiological studies on acrylamide. They found that these studies lacked the statistical strength to identify cancer risks associated with dietary acrylamide exposure at levels indicated by toxicological research.[17]

31. It is very important to assess the level acrylamide rich foods exposure to consumers in terms of understanding the potential health risks of acrylamide and developing new mitigation strategies for the future. The European Commission[9] and Joint FAO/WHO Expert Committee to Food Additives (JECFA)[2,3,7,8] reported that the studies on the exposure and risk assessments arising from acrylamide-contaminated foods are not sufficient and there is a need for systematic and comprehensive studies in this context.

32. In view of this, many countries and researchers have investigated risk analysis for dietary acrylamide exposure and consequent adverse health effects. Researchers have reported dietary acrylamide exposure to human from different foods was determined to be 0.43 µg/kg bw/day in Poland, 0.22 µg/kg bw/day in Türkiye, and 0.38 µg/kg bw/day in the Portugal[12] 0.5 ug/kg/bw/day in Sweden, 0.4 ug/kg/bw/day in USA, 0.3- 0.4 ug/kg/bw/day in Canada and 0.166 ug/kg/bw/day. While infants and children are the most vulnerable group mostly exposed to acrylamide (average acrylamide intake 0.5–1.9 µg/kg bw/day), and infant formulas have a significant share in this exposure at least twice the adult exposure.[12]

33. In the EFSA 2015 report,[12] it was stated that the mean acrylamide exposure in young, adult, elderly and older groups ranged between 0.4 and 0.9 µg/kg bw/day.

JECFA ASSESEMENT

34. At 64th JECFA meeting committee concluded that Margins of Exposure (MOEs) were calculated at intake levels of 0.001 mg acrylamide/kg bw/d (representing average intake) and 0.004 mg acrylamide/kg bw/d (representing intake by high consumers). Comparing these with the NOEL (non-observed effect level) of 0.2 mg/kg bw/d for nerve changes in rats yielded MOEs of 200 and 50, respectively. Comparison with the NOEL of 2.0 mg/kg bw/d for reproductive and developmental effects provided MOEs of 2000 and 500, respectively.

35. At the 72nd JECFA meeting $BMDL_{10}$ (the lower limit on the benchmark dose for a 10% response) of 0.31 mg/kg bw/d for mammary tumours in rats resulted in MOE of 310, and 78. It also concluded $BMDL_{10}$ of 0.18 for Harderian gland tumours in mice resulted in MOE of 180 and 45 respectively (Annexure 1, Table 2).[3,8]

[16] *Code Of Practice for the Reduction of Acrylamide in Foods* (CXC 67-2009)

[17] Joint Institute for Food Safety and Applied Nutrition (JIFSAN). JIFSAN 2004 Acrylamide in Food Workshop summary report on exposure and biomarkers.

36. Based on these findings, adverse effects at average intakes are unlikely, but nerve changes cannot be excluded for high consumers. JECFA made the following recommendations: (1) Acrylamide should be re-evaluated when results of ongoing carcinogenicity and long-term neurotoxicity studies become available,[18] (2) work should be continued on using pharmacologically based pharmacokinetic (PBPK) modelling to better link human biomarker data with exposure assessments and toxicological effects in experimental animals, (3) appropriate efforts to reduce acrylamide concentrations in food should continue, and (4) it would be useful to have occurrence data on acrylamide in foods as consumed in developing countries.[5]

37. According to recent studies, risk assessment of dietary AA intake in Japan it has low non-neoplastic risk. Margins of exposure (MOEs) for the non-neoplastic effects of AA were estimated based on the reference pointing $BDML_{10}$ of 0.43 mg/kg/bw/d and for neoplastic effects is 0.17 mg/kg/bw/d in mice and 0.3 mg/kg/d in rats.

38. AA being genotoxic and carcinogenic nature the margin of exposure is 260-960 raised a serious health concern[2,3,7-12] and suggested to continue with appropriate efforts to reduce the acrylamide in food stuffs.

39. Due to its toxicity, the World Health Organization (WHO)[8] had suggested a maximum residue limit (MRL) for drinking water at 0.5 lg/l and the European Commission (COM) as well as to fix its new MRL for AA in drinking water at 0.1 lg/l.[19]

RISK MANGEMENT CONSIDERATIONS

40. Global research initiatives were taken up by Joint FAO/WHO[18] where the discussion paper of AA[5] and code of practice of AA[16] provided strategies for prevention and control of AA in foods.

41. Complete elimination of AA is impossible while several developing countries have strategies to mitigate AA during food processing which includes storage conditions of potato that lead to reduce level of sugars, utilization of enzyme such as asparaginase, amino acids, calcium salts, reducing leavening agents for baked product, increasing fermentation time with yeast. [5,16]

42. Research studies suggested that these implementations effectively reduce the content of AA in foods. Further effective monitoring of the AA content in the foods evaluate the effectiveness of the strategy has been initiated by EU[19] member states,[20] Canada,[21] US.[22]

43. This includes assessment high content AA containing foods such as coffee, breakfast cereals, potato chips, cookies, bread, including cookies targeted to infants, and crackers and mitigation studies are reported in Acrylamide Tool Box.[23]

44. In addition, monitoring the environment for AA content for its persistence due to release form synthetic dyes, polymers, adhesives, paper/board, textile additives etc.

45. Canadian surveillance report of a total of 2284 samples were tested for acrylamide. Of these samples, 87% (1983) had detectable levels of acrylamide content.[21]

46. USFDA reported that significant decrease in levels of acrylamide levels in potato chips and crackers and observed that various food categories showed no significant decrease from 2011 to 2015 compared to the earlier period 2002-2006. It recommended for continuous risk management measures to prevent and control of the acrylamide content in foods.[22]

[18] FAO-WHO. FAO-WHO Acrylamide in Food Network (Acrylamide Infonet). http://www.acrylamidefood.org/index.htm. 2004.
[19] European Commission. Council directive 98/83/EC of 3 November 1998, On the quality of water intended for human consumption. Official journal of the European Communities L330, 21-29 (1998).
[20] COMMISSION REGULATION (EU) 2017/2158 establishing mitigation measures and benchmark levels for the reduction of the presence of acrylamide in food
[21] Health Canada's Revised Exposure Assessment of Acrylamide in Food, August 2012
[22] Eileen Abt Eileen et al., Acrylamide levels and dietary exposure from foods in the United States, an update based on 2011-2015 data, Food Additives & Contaminants: Part A 2019, DOI: 10.1080/19440049.2019.1637548
[23] Acrylamide Tool Box 2019 and at http:// ec.europa.eu/food/food/chemicalsafety/contaminants/acrylamide_en.htm

CONCLUSION

47. Risk assessment of AA and code of practice to prevent and control AA in foods was taken up by JECFA earlier and it has recommended to continue the efforts on occurrence, dietary exposure to invade the possible extent of AA. Several countries have reported occurrence data and implemented the risk management measures on AA in foods. While detailed assessment of mitigation measures effectiveness and enable feasibility for code of practices to other countries and propose revision of if any for prevention and control for other traditional foods of different countries.

RECOMMENDATION

48. CCCF is invited to:

    a. consider if the discussion paper needs further development. CCCF and members are requested to identify the gaps or information developed in order to guide the work of EWG.

    b. to request the JECFA Secretariat to issue as new call for data (a) long term toxicity studies (b) occurrence (c) dietary exposure data (d) monitoring or surveillance data.

    c. request members to share recommendations and suggestions on risk management measures, investigation of the evidence of long-term toxicity studies data.

Annexure I

Table 1: Summary Reported values for Acrylamides in foods (µg/kg) in the different food samples from different countries (WHO GEMS Database)

Food Categories	Commodity	N	Year	Country	Positive Samples	Maximum (µg/kg)	Average	Reference
Cereals and cereal-based products	Bread & other cooked cereal products	50	2005, 2007-08	Euro, EU, WPRO	48	65.9	29.30	WHO
	Cereal Grains	13	2005, 2007-08	Euro, EU, WPRO	10	29.2	15.85	WHO
	White Bread	04	2007-08	Euro, EU	2	11.6	11.6	WHO
	Whole Meal Bread	04	2007-08	Euro, EU	04	48.3	38.3	WHO
	Barley	01	2005	WPRO	0	-	-	WHO
Composite food (including frozen products)	Cereal-based dishes	50	2007-09	Euro, EU	24	80.5	27.25	WHO
	Meat-based meals	04	2007-08	Euro, EU	04	38.3	33.85	WHO
	Potato based dishes	08	2008-09	Euro, EU	04	13.9	6.95	WHO
Fish and other seafood (including amphibians,	Fishes	32	2007-09	Euro, EU	16	30	8.56	WHO
Fruit and fruit products	Apple	04	2007-08	Euro, EU	00	-	-	WHO
	Fruit and fruit products NES	04	2007-08	Euro, EU	00	-	-	WHO
Meat and meat products (including edible offal)	Chicken meat	04	2007-08	Euro, EU	00	-	-	WHO
	Turkey meat	08	2007-08	Euro, EU	02	46.2	11.55	WHO
Non-alcoholic beverages (excluding milk, fruit and vegetable juice, water and stimulants)	Cocoa beverage	28	2007-09	Euro, EU	28	30	21.76	WHO
Snacks and desserts	Snack food	52	2007-09	Euro, EU	52	1286.8	679.11	WHO
	Ices and desserts	40	2007-08	Euro, EU	20	53.9	14.32	WHO
Starchy roots and tubers	Potato	34	2005, 2007-09	Euro, EU,WPRO	32	1583.7	724.93	WHO
	Sweet potato	01	2005	WPRO	0	-	-	WHO
Stimulant beverages, dried and diluted	Coffee (Beverage)	36	2007-09	Euro, EU	26	245	67.13	WHO
	Coffee beans, roasted	01	2005	WPRO	0	-	-	WHO

excluding cocoa products	Tea and Hebral Tea (solid)	01	2005	WPRO	0	-	-	WHO
Sugar and confectionary (including cocoa products)	Cocoa mass	14	2007-058	Euro, EU	14	171.5	80.54	WHO

Note that: The levels of acrylamide in traditional Indian fried snacks, which are cereal and pulse-based, ranged from 22.0 to 361 µg/kg, while in confectionery items, the range was between 137.3 and 1420.6 µg/kg. Among traditional sweets, acrylamide content was lowest in Jamun (137.3 µg/kg) and highest in Kajjaya (1420 µg/kg). In Saudi Arabia acrylamide was found in ranging from 28 to 954 µg/kg, with salted chips containing the highest amount (954 µg/kg) and labneh and mint flavoured chips having the lowest (28 µg/kg). The results indicate significant variation in acrylamide content, likely influenced by factors such as food type, cooking ingredients, methods, and cooking time and temperature.

Table 2: Summary of toxicological evaluations of Acrylamide according 64th and 72nd JECFA meeting where dietary exposure estimates: mean: 0.001 mg/kg (bw) per day and High: 0.004 mg/kg bw per day.

Effect	NOAEL/$BMDL_{10}$ (mg/kg/ bw per day)	Mean Dietary exposure	High dietary exposure
Morphological changes in nerves in rats	0.2 (NOAEL)	200	50
Reproductive, developmental and other non-neoplastic effects	2.0 (NOAEL)	2000	500
Mammary tumours in rats	0.31 ($BMDL_{10}$)	310	78
Harderian gland tumours in mice	0.18 ($BMDL_{10}$)	180	45

$BMDL_{10,}$ lower limit on the benchmark dose for a 10 % response; bw, body weight, MOE, margin of exposure; NOAEL, no-observed adverse effect level.