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SCIENTIFIC REPORT OF EFSA

Endogenous formaldehyde turnover in humans compared with exogenous contribution from food sources[1]

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ABSTRACT

The FEEDAP Panel received a request to deliver a scientific opinion on the safety and efficacy of formaldehyde used in feed for all animal species based on dossiers submitted by applicants. In parallel, the ANS Panel evaluated the safety of formaldehyde formed from endogenous production and from dietary sources of methanol, including aspartame. In order to support both evaluations, assistance was requested to the SCER unit to evaluate the oral internal dose of formaldehyde in humans from endogenous production, food-derived from target animals exposed to formaldehyde-treated feed and formaldehyde generated from dietary sources of methanol, including from food additives such as aspartame. Endogenous turnover of formaldehyde was estimated to be approximately 0.61-0.91 mg/kg bw per minute and 878-1310 mg/kg bw per day assuming a half life of 1-1.5 min. Compared with formaldehyde turnover and the background levels of formaldehyde from food sources (1.7-1.4 mg/kg b. w per day for a 60-70 kg person), including from dietary methanol, the relative contribution of exogenous formaldehyde from consumption of animal products (milk, meat) from target animals exposed to formaldehyde-treated feed was negligible (<0.001 %). Oral exposure to formaldehyde from aspartame involves metabolism to methanol and further oxidation to formaldehyde. At the current ADI of 40 mg/kg bw per day for aspartame, formaldehyde would be approximately 4 mg/kg bw per day and represent only 0.3-0.4 % of the endogenous turnover of formaldehyde.

KEY WORDS

formaldehyde, endogenous, background levels, carry-over, aspartame, methanol

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SUMMARY

Formaldehyde is an important metabolic intermediate that is physiologically present in all cells. The electrophilic nature of formaldehyde makes it reactive towards a variety of endogenous molecules, including glutathione, proteins, nucleic acids and folic acid.

In order to estimate the synthesis and metabolism of formaldehyde in the human body, authors in the scientific literature have assumed that it is present in all aqueous body fluids because of its water solubility and have estimated its half life in humans as 1-1.5 min. Blood and intracellular steady state concentrations of formaldehyde have been estimated in humans to be around 2.6 mg/L (87 µM) and 12 mg/L (400 µM), respectively. Based on blood steady state concentrations and half life values in humans of 1-1.5 min, formaldehyde turnover was estimated to be approximately 0.61-0.91mg/kg bw per minute corresponding to a daily turnover of 878-1310 mg/kg bw per day.

Background levels in food products of formaldehyde are very variable and range from values around 0.1-0.3 mg/kg in milk to over 200 mg/kg in some fish species. Considering such wide variability in formaldehyde concentrations and assuming a person would be eating one kilogram of food per day, it was assumed that oral exposure to formaldehyde in humans would not exceed 100 mg formaldehyde per day, corresponding to 1.7 and 1.4 mg/kg bw per day for 60 kg and 70 kg respectively. Carry over in animal tissues has been measured in a few limited tissue deposition studies, mostly in cows and the data showed a maximum increase in formaldehyde concentration between 0.1-0.2 mg/kg milk or meat. Such levels of formaldehyde resulting from the consumption of milk or meat from animals fed with formaldehyde-supplemented feed would represent 0.1-0.3 % of human oral exposure from background levels in food products and would be below 0.001 % considering the endogenous formaldehyde turnover. Such levels were considered negligible.

Based on the analysis of the EFSA Scientific Panel on Food Additives and Nutrient Sources added to Food using actual usage data, methanol from aspartame was estimated to contribute to 0.5-9.7 % of the total daily exposure to endogenous and exogenous methanol. For formaldehyde, and assuming exposure to aspartame at the current Acceptable Daily Intake of 40 mg/kg bw per day together with a 10 % conversion to methanol with further conversion to formaldehyde, a daily exposure of 4 mg/kg bw per day is estimated. This exposure would only contribute to approximately 0.3-0.4 % of human oral exposure from background levels in food products and endogenous turnover.

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BACKGROUND AS PROVIDED BY EFSA

Formaldehyde, a known carcinogen, is currently being considered in ongoing evaluations by the ANS and FEEDAP Panels. The ANS Panel has re-evaluated, among others, the artificial sweetener aspartame that forms formaldehyde as part of its metabolism (EFSA-Q-2011-00406). The FEEDAP Panel is currently evaluating formaldehyde as a preservative for feed, and their terms of reference include both consumers and users and target species (EFSA-Q-2013-00763). In addition, both the ANS Panel and the FEEDAP Panel are re-evaluating hexamethylenetetramine (EFSA-Q-2011-00458 and EFSA-Q-2012-00415), that is also partially metabolised to formaldehyde. The SCER unit has produced an internal report resulting from an assistance request from the FEEDAP and the FIP unit. The report evaluated the internal exposure to formaldehyde in humans from food derived from target animals exposed to formaldehyde-treated feed and compare this to (i) the endogenous production of formaldehyde and (ii) the internal exposure to formaldehyde from aspartame and other dietary or endogenous sources (performed by the ANS Panel).

TERMS OF REFERENCE AS PROVIDED BY EFSA

The SCER unit is requested to produce a scientific report from the internal report on “endogenous formaldehyde synthesis and metabolism in humans compared with exogenous contribution from food sources”, by 31 January 2014. In order to follow the EFSA procedure for scientific reports, the SCER unit should have the report reviewed by at least two external reviewers with relevant expertise.

ASSESSMENT

1. Introduction

This Scientific report summarises the scientific support provided by the SCER unit after receiving an assistance request from the FEEDAP and FIP unit, for the evaluation and comparison of the internal dose to formaldehyde in humans from endogenous turnover, background levels in food, food-derived from target animals exposed to formaldehyde-treated feed and formaldehyde derived from aspartame-derived methanol.

2. Endogenous turnover of formaldehyde in humans

Formaldehyde is an essential metabolic intermediate estimated from measurements in nasal tissue to be present in cells at an intracellular concentration of around 12 mg/L (400 µM) (EFSA, 2013). There are numerous sources of endogenous formaldehyde including the one carbon pool, amino acid metabolism (serine, glycine, methionine, and choline), methanol metabolism, lipid peroxidation, and P450 dependent demethylation (e.g. O-, N-, and S-methyl) (Dhareshwar and Stella, 2008; Swenberg et al., 2011). The metabolism of formaldehyde is rapid and catalysed by glutathione-dependent formaldehyde dehydrogenase (which is also known as alcohol dehydrogenase 5, ADH5) and S-formyl-glutathione hydrolase to formic acid. Formic acid then enters the one-carbon pool where it can be incorporated as a methyl group into nucleic acids and proteins and is either excreted in the urine or oxidised to carbon dioxide and exhaled at a significantly slower rate than its formation from formaldehyde (formic acid halflife in plasma is between 1 and 6 h) (Dhareshwar and Stella, 2008). ADH5 has been detected in all human tissues at all stages of development, from embryo through adult. The electrophilic nature of formaldehyde makes it reactive towards a variety of endogenous molecules, including glutathione, proteins, nucleic acids and folic acid. (NTP, 2011). Ideally, an evaluation of the fate of formaldehyde in vivo requires a distinction between products which are normal cellular metabolites, those which are detoxification products and those which are formed chemically in localized tissues due to the reactivity of formaldehyde (Dhareshwar and Stella, 2008).

Formaldehyde concentration in the blood of mammals resulting from endogenous production is similar in different species with 2.2, 2.4 and 2.6 mg/L in the rat, monkey and humans, respectively (Heck et al., 1982; 1985; Casanova et al., 1988). In order to estimate the total content of formaldehyde in the human body, authors have assumed that it is present in all aqueous body fluids because of its water solubility and have estimated its half life in humans as 1-1.5 min (Sullivan and Krieger, 2001) with a volume of distribution as approximately total body water (42 and 49 L for an adult of 60 and 70 kg, respectively), giving a total body content of 1.82 mg/kg bw and using the steady state concentration of 2.6 mg/L. Based on the latter total body formaldehyde content and the reported half-lives of 1 and 1.5 min (Clary and Sullivan, 2001), there would be a turnover of 0.61-0.91 mg formaldehyde/kg bw per minute or 878-1310 mg formaldehyde/kg bw per day to maintain a formaldehyde steady state concentration of 2.6 mg/L in the blood stream (Cascieri and Clary, 1992; Dhareshwar and Stella, 2008).

3. Background levels of formaldehyde in food

Background levels of formaldehyde have been measured in milk, meat, plant material, mushrooms and fish.

Formaldehyde is present in the milligram range with the lowest level measured in fresh milk (0.013 - < 1 mg/kg) (Kaminski et al. 1993; Trezl et al., 1997).

In pig tissues, background formaldehyde levels (n=3) has been measured with values of 11.8±0.17, 8.75±0.28, 6.24±0.12 mg/kg in liver, kidney and muscle, respectively (Retfalvi et al., 1998). In meat, background levels of formaldehyde ranged from 2.5 mg/kg in sandwich paste from poultry, 2.9-4.6

mg/kg in cold meat cuts, ham from poultry, turkey, up to 10-20.7 mg/kg in sausages and up to 224-267 mg/kg in the outer layer of smoked ham (Brunn and Klostermeyer, 1984; Trezl et al., 1997).

In fish, formaldehyde background levels show the highest values measured in food with extreme values 232-293 mg/kg in deep frozen hake, lowest values in haddock and mullet 1.47-4.87 mg/kg and average values in cod around 100 mg/kg (Bianchi et al. 2007; Weng et al. 2009). It has been noted that the post-mortem formation of formaldehyde in fish is the result of the reduction of trimethylamine-N-oxide to formaldehyde and dimethylamine (Sotelo et al., 1995; Badii and Howell, 2002)

In plant material such as fruit vegetables, background formaldehyde levels (mg/kg) range from 6.3 and 6.8 in apples and carrots, 9.0 in fresh water melon, 9.5 in apricot to 13.3 in tomatoes, 16.3 in bananas, 19.5 in potatoes to 26.9, 31 and 35 in cauliflower, kohlrabi and large beetroot respectively (Trezl et al., 1997).

From these figures, background levels in food products of formaldehyde are very variable and range from values below1 mg/kg in milk to over 200 mg/kg in some fish species (Kaminski et al., 1993; Trezl et al., 1997; Bianchi et al., 2007; Dhareshwar and Stella, 2008; Weng et al., 2009). Providing a precise exposure assessment was not the purpose of this report but assuming a person would be eating one kilogram of food per day (including milk, fish, meat, ham, vegetables, fruit) and giving of the variability of background formaldehyde concentration in raw commodities and food products, it was assumed that oral exposure to formaldehyde in humans from dietary sources would not exceed 100 mg formaldehyde per day corresponding to 1.7 and 1.4 mg/kg bw per day for 60 kg and 70 kg respectively. It should be noted that these exposure estimates do not include endogenously produced formaldehyde from dietary and endogenous sources of methanol. Table 1 summarises the background levels of formaldehyde in a range of food commodities as described in literature.

Table 1: Background levels of formaldehyde in food

Food Product	**Formaldehyde content mg/kg**
Meat and poultry	5.7-20
Fish	6.4-293
Milk and milk products	0.01-0.80
Sugar and sweeteners	0.75
Fruit and vegetables	6-35
Coffee	3.4-16
Alcohol beverages	0.27-3.0

4. Tissue deposition studies of formaldehyde in animal species

Few tissue deposition studies investigating the internal dose of formaldehyde in the bloodstream of animal species after supplementation of feed treated with formaldehyde were available. In cows, Buckley et al. (1988) supplemented whey forage with formaldehyde at increasing levels ranging from 0, 185, 370 or 555 mg /kg whey given to cows at 75 kg per day corresponding to 13900, 27800, 41600 mg per cow, respectively, or 21.4, 42.8, 64 mg/kg bw per day for a 650 kg cow. Overall, maximum formaldehyde levels in the milk of cows receiving 0, 21.4, 42.8 and 64 mg/kg bw per day for 33 days were < 0.026 mg/kg (below limit of detection), 0.052, 0.094 and 0.193 mg/kg giving maximum incremental increase of formaldehyde in milk of 0.02,0.07, 0.17 mg/kg milk. In addition, the authors concluded that it was likely that storage and pasteurisation of milk resulted in a reduction of free formaldehyde through irreversible binding to milk protein. Average blood concentration in cows was also measured and was only slightly higher at 64 mg/kg bw per day after 33 days but not significant ($P>0.05$) compared with controls (0.831 vs 0.615).

In addition, a trial was performed in 6 calves per treatment (0, 24.1 and 45.0 mg/kg bw per day (average) calves or 185 and 370 mg/kg feed respectively) for 95 days and two calves from each treatment group were slaughtered at days 81, 88, and 95 days after the beginning of the trial. Tissue samples of heart, kidney, liver, and muscle (*M. longissimus dorsi*) were collected and frozen until subjected to formaldehyde analysis (limit of detection 0.026 mg/kg) The only significant difference between control and the highest dose group ($P<0.05$), was found for the muscle (0.256 mg/kg vs 0.158 mg/kg, respectively for the 45.0 mg/kg bw per day (370 mg/kg) versus controls) but for no other organs (heart, kidney, liver) or blood levels. It is worth noting that there is considerable uncertainty in the data since only two animals per group were used (Buckley et al., 1988).

In another study, five grams of formaldehyde per day from formaldehyde treated soybean meal was administered to dairy cows in a 10 week feeding study and an slight increase in the formaldehyde concentration of milk from initial 0.023 - 0.039 mg/L to 0.095 - 0.114 mg/L (three weeks) and to 0.25 mg/L after 10 weeks (Pinault, 1989, cited from AFSSA, 2004). This data gives an incremental increase of 0.1 mg/L after three weeks and around 0.2 mg/L of milk after 10 weeks.

A 12-month feeding study in beef cattle administered 1 g formaldehyde/day from formalin treated soybean meal showed a slight increase in formaldehyde muscle content from 0.065 mg/kg to 0.167 mg/kg (incremental increase of 0.102 mg/kg) (Pinault, 1989, cited from AFSSA, 2004).

From the limited studies available describing formaldehyde deposition in animal-tissues or milk and muscle after supplementation of feed with formaldehyde, it can be concluded that formaldehyde concentrations in milk and muscle have been shown to increase slightly (0.1-0.2 mg/L milk and muscle at minimum levels of exposure >300 mg formaldehyde per kg feed with a minimum of 33 day of exposure). Such levels are well below the background levels of formaldehyde in food (0.1-0.3 %).

5. Comparison of endogenous formaldehyde with oral exposure from food sources

5.1. Endogenous formaldehyde versus background levels in food and carry over from animal products

The turnover of endogenous formaldehyde to maintain the human blood steady state concentration of 2.6 mg/l has been estimated to be approximately 0.61-0.91 mg/kg bw per minute equivalent to 878-1310mg/kg bw per day for half lives of 1-1.5 min. (Section 2).

Background levels of formaldehyde have been shown to be very variable in food ranging from <0.1 mg/kg in milk to >200 mg/kg in fish) and taking a consumption scenario of 1 kg of food per person (including milk, fish, meat, ham, vegetables, fruit), it was assumed that oral exposure to formaldehyde in humans from background levels in food would not exceed 100 mg/kg food per person per day corresponding to 1.7 and 1.4 mg/kg bw per day for a 60 kg and 70 kg person, respectively (Section 3).

Carry over in animal tissue or products of formaldehyde has been measured in a few limited tissue deposition studies mostly available in cows and showed that the maximum increase in formaldehyde concentration was between 0.1-0.2 mg/kg milk or meat (muscle) (Section 4). Such levels of formaldehyde resulting from the consumption of milk or meat from animals fed with formaldehyde-supplemented feed would represent 0.1-0.3 % of human oral exposure to formaldehyde from background levels of formaldehyde in food products (100 mg person per day or 1.7 and 1.4 mg/kg bw per day for 60 kg and 70 kg person) and would be below 0.001 % considering the daily turnover of formaldehyde (874-1310 mg/kg bw per day). Such levels were considered negligible.

5.2. Aspartame-derived methanol/formaldehyde versus endogenous and background levels in food

With regards to aspartame, the Scientific Panel on food additives and nutrients in its scientific opinion on the re-evaluation of aspartame has discussed that aspartame is partially metabolised into methanol

(10 % of a dose per weight) which is then further oxidised sequentially to formaldehyde by alcohol dehydrogenase in humans, formic acid or formate in a pH-dependent manner and finally to carbon dioxide (EFSA, 2013). Endogenous methanol production also occurs and the Panel estimated the basal endogenous methanol production to range from a minimum of 2 to a maximum of 9 mg/kg bw per day in adults. In addition, pectin degradation from fruit and vegetables has been shown to be a source of methanol and the Panel has estimated that the body increases in methanol production following consumption of pectin-containing foods such as apples would range by an additional 6-20 mg/kg bw per day. On a daily basis, endogenous methanol and methanol from pectin degradation would range from 8 to about 34 mg/kg bw per day (mean to high level exposure) (EFSA, 2013). Based on actual usage data, methanol from aspartame (8-34 mg/kg b.w per day) only contributes 0.5-9.7 % of the total exposure to methanol from endogenous and exogenous sources (EFSA, 2013). Assuming exposure to aspartame at the current Acceptable Daily Intake (ADI) of 40 mg/kg bw per day and a 10 % conversion to methanol additional exposure to methanol (4 mg/kg bw per day) would be well below endogenous and background levels in food (2 to 9-fold). Further conversion of methanol to formaldehyde would yield a daily exposure of 4 mg/kg bw per day, which would only represent 0.3-0.4 % of the total formaldehyde exposure, based on a daily turnover of formaldehyde of 878-1310 mg/kg bw per day (EFSA, 2013).

CONCLUSIONS

- Formaldehyde is an essential metabolic intermediate present in all cells at an intracellular concentration of around 400 µM (12 mg/L) which is synthesised endogenously. Sources of endogenous formaldehyde include the one carbon pool, amino acid metabolism, methanol metabolism, lipid peroxidation, and P450 dependent demethylation.
- Formaldehyde metabolism is rapid and catalysed by glutathione-dependent formaldehyde dehydrogenase and S-formyl-glutathione hydrolase to formic acid. Formic acid then enters the one-carbon pool and is either excreted in the urine or oxidised to carbon dioxide and exhaled. The electrophilic nature of formaldehyde makes it reactive with a variety of endogenous molecules, including glutathione, proteins, nucleic acids, and folic acid.
- Formaldehyde concentration in the blood of mammals resulting from endogenous production is similar in different species with 2.2, 2.4 and 2.6 mg/L in the rat, monkey and humans respectively. Formaldehyde half life in humans is very short and has been estimated to be within 1-1.5 min associated with a volume of distribution approximately corresponding to total body water (49 L). Total content of formaldehyde in the human body has been estimated assuming its presence in all aqueous body fluids and a range of half-lives of 1 and 1.5 min, daily endogenous turn over of formaldehyde has been estimated to be around 878-1310 mg/kg bw per day.
- Background levels in food products of formaldehyde are very variable and range from values below 1 mg/kg in milk to over 200 mg/kg in some fish species. Considering the wide variability of formaldehyde concentrations in food, daily exposure to formaldehyde from would not exceed 100 mg per kilogram of food and per person.
- Carry over in animal tissue or products of formaldehyde has been measured in a few limited tissue deposition studies mostly available in cows and showed a maximum increase in concentration between 0.1-0.2 mg/kg milk or meat (muscle). The levels of formaldehyde resulting from the consumption of milk or meat from animals fed with formaldehyde-supplemented feed would be around 0.1 % of the background levels of formaldehyde in food products and below 0.001 % of daily endogenous turnover of formaldehyde. Such levels are considered negligible.
- Oral exposure to formaldehyde derived from aspartame-derived methanol at the current acceptable daily intake of aspartame would be 4 mg/kg bw per day assuming a 10 % conversion. Such exposure only represents 0.3-0.4 % of the combined background level in food and the daily turnover of formaldehyde for an adult.

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ABBREVIATIONS

ADI	Acceptable daily intake
ANS	Scientific Panel on Food Additives and Nutrient Sources added to Food of the European Food Safety Authority
EFSA	European Food Safety Authority
SCER	EFSA's Scientific Committee and Emerging Risks Unit
FEEDAP	Scientific Panel on Additives and Products or Substances used in Animal Feed of the European Food Safety Authority
FIP	EFSA's Food Ingredients and Packaging's Unit