TOXICOLOGICAL ASSESSMENT OF ASPARTAME: FOCUS ON THE METABOLITE *METHANOL*

Alberto Mantovani, Leonello Attias
Istituto Superiore di Sanità- Rome ITALY
On behalf of the Italian National Food Safety Committee
(CNSA)
alberto.mantovani@iss.it

NATIONAL FOOD SAFETY COMMITTEE
(*Comitato Nazionale Sicurezza Alimentare, CNSA*)

An independent scientific body (15 members plus secretariat) appointed by the Minister of Health

Members belong to public health/research institutes and universities, are nominated on the basis of recognized scientific prowess in different fields relevant to food safety (zoonoses, human nutrition, epidemiology, toxicology..)

TASKS

To provide independent advice on food safety-relevant issues (questions from Health Ministry, self-tasking)

To support EFSA activities, e.g., by providing inputs to scientific consultations, such as that on

ASPARTAME

The draft opinion by the ANS Panel is a *valuable and accurate* document; it deserves merit

CNSA endorses the attention on toxicity and internal exposure to *major aspartame metabolite, phenylalanine*

CNSA wishes to draw attention toward some points of the assessment of *another main aspartame metabolite*, METHANOL.

What is the contribution of methanol from aspartame intake to the total methanol intake (endogenous, naturally present in foods, from fruit pectins) ?

Calculations are presented in *table 12 of the Draft Opinion*

BUT

We deem that these are unclear, and some might be wrong,

i.e., the exposure ranges for average and high-consuming toddlers. We recommend to provide a more clear rationale for the calculations in table 12

Exposure range of methanol from basal endogenous pathway are derived from values in adults. As pointed out also by the draft opinion, this could lead to *underestimation* in toddlers and children and *overestimation* in the elderly

calculated exposure ranges for toddlers (*incorrect ?*):
reported total exposure range (mean) 14.7-18.9 mg/kg bw/d whereas it should be 13.9-21.0 mg/kg bw/d;
(high level) 26.3-35.1 mg/kg bw/d, should be 26.3-38.8.
These are not just details (see next slides)

	Toddlers		Children		Adolescents		Adults		The elderly	
	Mean	High level	Mean	High level	Mean	High level	Mean	High level	Mean	High level
	mg/kg bw/day									
Exposure range of methanol from basal endogenous pathway	5.5[a]	9	5.5	9	5.5	9	5.5	9	5.5	9
Exposure range of methanol from endogenously metabolised pectin	7.9-12.5	15.2-24.1	3.9-10.5	7.7-20.0	2.1-5.0	5.3-10.5	2.4-4.2	5.1-7.9	3.0-4.5	6.0-8.1
Exposure range of methanol from natural food occurrence	0.2-1.4	0.9-3.8	0.3-1.4	0.9-3.3	0.2-0.6	0.6-1.4	0.3-0.6	0.7-1.6	0.2-0.6	0.6-1.4
Exposure range of methanol from all endogenous pathways (basal, endogenously and metabolised pectin) and natural food occurrence	**13.8-18.4**	**9.0-33.1**	**9.8-17.4**	**20.3-36.8**	**8.0-10.7**	**14.3-19.5**	**8.2-10.3**	**14.1-16.9**	**8.9-10.6**	**15.0-17.1**
Exposure range of methanol from aspartame as a food additive (using MPLs)	0.3-1.6	1.2-3.7	0.2-1.3	0.7-3.3	0.1-0.4	0.2-1.3	0.1-0.9	0.3-2.7	0.05-0.4	0.2-2.4
Total anticipated exposure to methanol from all sources (endogenous pathways (basal, endogenously metabolised pectin) and natural food occurrence and aspartame as a food additive)	**14.7-18.9**	**26.3-35.1**	**10.4-17.6**	**18.1-31.8**	**8.4-11.0**	**15.5-20.2**	**8.4-10.3**	**15.1-18.2**	**9.0-10.7**	**15.8-17.9**

Methanol toxicology is under discussion within REACH

ECHA website: a *short term and long term oral DNEL of 8 mg/kg bw/day* for general population.

Human data, mainly but not only occupational exposure

Short- term, non-fatal neurotoxic effects **including ocular nerve toxicity.**

DNELs reported in ECHA are extracted from the registration dossier *provided by industry and not derived from an independent assessment.*

Why a specific attention within REACH ?

methanol is under evaluation for *developmental toxicity including teratogenicity* based on rodent studies showing malformations, including of brain.

Mechanism of teratogenicity may be associated to oxidative damage: however, extrapolation to human is under discussion.

Methanol is further metabolised to *formic acid*. This may be transferred through human placenta and may impair placental function: folic acid mitigates placental effects but not transfer

- developmental toxicity, especially teratogenicity, may result from *acute intake in a susceptible developmental window* (does not need chronic intake)

Given that the *internal exposure to phenylalanine from aspartame* and its developmental effect are *critical* for aspartame risk characterisation…

Can we rule out completely a *potential for additive developmental effects* of methanol and phenylalanine?

Even considering *all the uncertainties* inherent to the current DNELs for methanol,
it is worth noting that the calculated intakes from *endogenous pathways and natural food occurrence only* (as reported in table 12) are all above 8 mg/kg bw/day.

Therefore it might be sensible to recommend that methanol intake from aspartame as food additive *should not add significantly* (e.g. no more than 10%) to the background intake.

Based on the calculations reported in table 12, in some instances (e.g. *high level elderly*) the intake of methanol from aspartame as a food additive (using MPLs) *seems to add more than 10% to the background intake*.

Final recommendations

- More comparative data on the internal exposure to all main aspartame metabolites in animal and human studies would support the extrapolation to human health of rodent studies on aspartame.

- ADI is unchanged since (SCF 1985) and based on rodent studies:
taking into account new data (human studies, kinetic, mechanistic, etc.) as well as uncertainties,
and the overall developmental NOAEL identified by the ANS Panel (Lines 139-140 of the summary)
"*1000 mg aspartame/kg bw/day* for maternal (weight loss) and developmental toxicity (weight loss and malformations)"

any need to *refresh the ADI*?

05/04/13