anses
French agency for food, environmental and occupational health & safety

The Director General

Maisons-Alfort, 27 September 2010

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

regarding the assessment of the claimed effects of a beverage on the reduction of blood alcohol levels

1. REVIEW OF THE REQUEST

On 12 July 2010, the French Agency for Food, Environmental and Occupational Health & Safety received a request from the Directorate General for Competition, Consumer Affairs and Fraud Control (DGCCRF) for an evaluation of the claimed effects of a beverage on the reduction of blood alcohol levels.

2. BACKGROUND

This request deals with the alleged claims for a non-alcoholic carbonated soft drink currently marketed in France. The beverage is supposed to accelerate a decrease in blood alcohol levels ("accelerates the natural decrease in the alcohol level") and to alleviate some of the harmful effects related to excessive alcohol consumption ("prevents hangovers").
From a regulatory viewpoint, this health claim is governed by Regulation (EC) No. 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. The evaluation by the European Food Safety Authority of a claim on the effects of a mixture of glucose and fructose on alcohol elimination in the liver is underway.

3. METHOD OF EXPERT ASSESSMENT

This dossier was studied internally with expert consultation, and the opinion was adopted by the Expert Committee (CES) on "Human Nutrition" by electronic validation on 22 September 2010.

4. DISCUSSION

ANSES's discussion is based on the opinion of the CES on "Human Nutrition", which includes the key points presented below.

4.1. Product characteristics

According to the applicant, the currently marketed beverage is composed of carbonated water, fructose, acidifiers (citric acid, malic acid), an antioxidant (ascorbic acid), flavourings, stabilizers and colouring agents. The applicant states the following composition per 100 mL:

- energy content: 82.8 kcal
- proteins: 0 g
- carbohydrates: 20.7 g (including sugars: 20 g)
- lipids: 0 g
- dietary fibre: 0 g
- sodium < 0.1 g

The claimed effect on the reduction of blood alcohol levels is reportedly based on the combination of fructose and ascorbic acid. According to the applicant, these nutrients supposedly act "on the liver to stimulate the production of enzymes that break down the alcohol through oxidation into CO_2 and water, which are then eliminated through natural routes. The physical phenomenon accelerates the elimination of alcohol and the return to the normal state."
In addition, this effect is reportedly supported by a recent study carried out on the beverage by an independent laboratory at the request of the applicant.

4.2. Literature review

4.2.1. Effects of fructose on blood alcohol levels

Many studies in animals and humans have analysed the effects of oral or intravenous (IV) fructose intake on the metabolism of ethanol.

Several studies in animals show that fructose reportedly increases the metabolism of ethanol. In two studies by Jones *et al.* (1979; 1983), the oral ingestion of fructose in rats, either alone or mixed with glucose, concurrent with or after ethanol ingestion decreased the peak plasma concentration of ethanol, the area under the curve of elimination and the time needed for its complete elimination from the body. Scholz *et al.* (1975) suggested that fructose might facilitate the action of alcohol dehydrogenase (ADH) by promoting the regeneration of nicotinamide adenine dinucleotide (NAD).

The results in humans, which were obtained in restricted population groups, are often contradictory, and a mechanism of action has not been clearly demonstrated.
Some studies show no effect from fructose on the ethanol elimination rate or on the intensity of symptoms of alcoholic intoxication (Ylikahri *et al.*, 1976; Levy *et al.*, 1977); others show an effect on the acceleration of alcohol metabolism. For example, Brown *et al.* (1970) showed that the IV injection of 200 g of fructose increased the mean rate of alcohol elimination by about 25% in patients with acute alcohol intoxication. Soterakis *et al.* (1975) showed that compared to glucose, orally administered fructose (2 g/kg bw) and sucrose (4 g/kg bw) in eight abstinent alcoholic subjects increased the elimination rate of alcohol injected by IV (0.19 g/L/h with the glucose, 0.24 g/L/h with the sucrose and 0.25 g/L/h with the fructose). In the study by Rawat *et al.* (1977), fructose increased the blood clearance of ethanol by nearly 100%. In 10 subjects who had consumed alcohol and fructose, the area under the curve, the maximum peak blood alcohol levels and the blood alcohol level at different evaluations were lower than with the placebo (Meyer 1982). Mascord *et al.* (1991) found that the mean rate of alcohol elimination (evaluated by the quantity of IV alcohol needed to maintain a stable blood alcohol level) increased by 80% after the oral ingestion of 100 g of fructose in 10 human volunteers. However, the inter-individual differences were considerable - ranging from a 13% reduction to a 300% increase.

4.2.2. Effects of ascorbic acid on blood alcohol levels

Studies conducted in guinea pigs show an effect of vitamin C on alcohol metabolism. Yunice *et al.* (1984) showed that the elimination rate of acute orally administered alcohol was higher in animals treated with vitamin C (by oral route; low dose - 200 ppm or high dose – 2000 ppm) compared to those receiving fructose or not receiving treatment. In cases of chronic alcohol intake (8 weeks), blood alcohol levels were lower in the animals that had received high doses of ascorbic acid. Ginter *et al.* (1998; 1999) showed that after acute or chronic alcoholisation, high vitamin C intake (0.5% w/w of the diet appeared to increase the metabolism of ethanol and acetaldehyde. Vitamin C reportedly induced dose-dependent activity of the hepatic enzymes involved in the metabolism of xenobiotics (Liu, 2000).
Clinical studies are rare and are based on small-sized samples. Susick *et al.* (1987) showed in 20 men that the intake of 5 g/day of ascorbic acid, i.e., 5 times the upper limit of intake, for two weeks significantly increased ethanol blood clearance (administered at 0.95 g/kg bw), as well as motor coordination in half of the subjects. Chen *et al.* (1990) also showed in 13 healthy men that a regular intake of ascorbic acid (2 g/day for 2 weeks) significantly increased the plasma clearance of alcohol.

ANSES notes that a number of studies suggest that fructose accelerates the oxidation of ethanol by the liver. The mechanism of action however has not been clearly demonstrated. The ability of fructose

to use H^+ ions produced by the oxidation of ethanol and therefore to regenerate NAD has been suggested, as have other mechanisms such as the slowing of alcohol absorption. Furthermore, these studies are often of limited methodological quality, and the fructose intakes are high (at least 1 g/kg bw).

Although some data in the literature suggest that fructose has a biological effect on alcohol absorption, particularly in animals, its biological significance in humans has not been demonstrated. On the one hand, the observed effect is of low magnitude. In the different studies showing an effect, the reduction in blood alcohol levels was around 10%. And yet, the risk of accidents increases exponentially with the blood alcohol levels, in an interval of 0 to 2.5 g/L and more. According to the Freudenberg Table (see Annex 1), a decrease of about 10% in blood alcohol levels, for levels between 0 and 1.5 g/L, does not produce a sufficiently large decrease in the risk of accident, whether fatal, bodily or material. On the other hand, the variance of this effect is high (Brown *et al.*, 1972). Therefore even if a significant mean effect can be observed in a group of individuals, the individual effect may differ.
In addition, ANSES notes that the risks linked to alcohol consumption are totally eliminated only for blood alcohol levels equal to zero.
Finally, these results should be considered with caution, since they are contingent on the experimental protocol used.

With regard to ascorbic acid, animal studies have been conducted exclusively in guinea pigs, and the results cannot be extrapolated to humans. Clinical studies are rare and are based on small population samples. Some of them suggest that ascorbic acid accelerates the metabolism of alcohol, but these results were obtained after regular vitamin C intakes over several days prior to the alcohol consumption, which is not consistent with the use of the product. In addition, as the ascorbic acid content of the product is not specified, it is not possible to evaluate a potential effect of the beverage in relation to its ascorbic acid content.

4.3. Evaluation of the study provided by the applicant

ANSES first emphasises that the study report does not specify the composition of the product that was used in the study. It is therefore not possible to guarantee that the evaluation of the legitimacy of the proposed claim can be transposed to the marketed product. Furthermore, it seems that this interventional study had not received clinical trial authorisation from the French Health Products Safety Agency (AFSSAPS).

4.3.1. Study protocol

This study included two parts: one based on the kinetics of the measured blood alcohol levels in exhaled air using a breathalyser test and the other on behavioural aspects.
The beverage used was described as an orange, non-alcoholic, moderately carbonated soft drink packaged in 250 mL cans.

➢ Kinetic study

The kinetic study was performed with an open label and intra-individual design, each subject being their own control. The participants were divided into two groups of 12 and 43 subjects, with equal numbers of men and women.
In Group 1 (12 subjects), the study compared the kinetics of the alcohol in the exhaled air between Day 0 (simultaneous consumption of alcohol and a placebo in two administrations) and Day 3 (simultaneous consumption of the same volume of alcohol and the product in two administrations). The second day of the protocol actually corresponded to Day 0 + 6 days. An alcohol volume of 6 cL in women and 8 cL in men was given at each administration, and a volume of 12 cL, i.e., half a can, was given for each administration of the product or placebo. The alcohol level in the exhaled air was measured using a breathalyser test on Day 0 and Day 6 at the following times:

- Before the first administration of alcohol
- 30 minutes after the first administration of alcohol (t_{30})
- 30 minutes after the second administration of alcohol (t_{30a})
- 45 minutes after the second administration of alcohol (t_{45})

In Group 2 (43 subjects), the study compared the kinetics of the alcohol in the exhaled air between Day 0 (consumption of alcohol alone in 4 administrations at 5 minute intervals) and Day 3 (consumption of the same volume of alcohol in 4 administrations, then one can of the product). The total volume of alcohol administered per day was 12 cL for women and 16 cL for men. The alcohol level in the exhaled air was measured using a breathalyser test on Day 0 and Day 3 at the following times:

- Before the administration of alcohol
- 30 minutes after the last administration of alcohol (t_{30})
- 45 minutes after the last administration of alcohol (t_{45})
- 60 minutes after the last administration of alcohol (t_{60})

The design of the trial for both groups is summarised in Annex 2.

➢ Behavioural study

Clinical scores for each participant were measured at the same time as the first and last breathalyser tests. A doctor assigned scores on a scale from 1 to 4 on general health condition, attention, concentration, alertness, immediate memory recall, responsiveness and orientation.
The participants also filled out an evaluation questionnaire on the organoleptic characteristics of the beverage, its efficacy, safety and its subsequent use.

ANSES notes that the protocol used does not meet the criteria of a standard pharmacokinetic study. The number of measurements of blood alcohol levels was actually insufficient for calculating the half-life and other common kinetic parameters.

ANSES indicates that the kinetics of alcohol elimination is not linear and follows a Michaelis-Menten model. This model includes four phases:

1. Non-linear absorption which reaches a peak at about 30 minutes on an empty stomach;
2. Rapid, exponential elimination for high blood alcohol levels (> 0.8-1 g/L);
3. Pseudo-linear elimination for moderate concentrations;
4. A slower exponential phase of elimination for concentrations below 0.3 g/L.

In the protocol used in Group 2 (administration of alcohol only), the highest concentration peak was reached in about ½ hour, which corresponds to the first measurement. The measurements at t_{45} and t_{60} were therefore relatively early compared with the total disappearance of alcohol from the body.
In the protocol used in Group 1 (2 administrations of alcohol at a 30 minute interval), the first measurement at t_{30} corresponds to the peak blood alcohol level of the first alcohol intake, and t_{30a} to the peak of the second administration coupled with the remainder of the first intake. T_{45} was a measurement made near the beginning of the exponential decay phase.
These measurements were therefore taken at times when the blood alcohol levels were most variable, thus complicating the interpretation of the results.
In addition, ANSES notes the lack of measurement in the pseudo-linear phase (3), which would have been easier to interpret, and would have enabled an assessment of changes in the product's effect over time.

With regard to the behavioural section of the study, ANSES notes that there had been no prior objective testing to standardise the rating scale. The evaluation of criteria was subjective, even more so as it used an open label methodology.

4.3.2. Statistical analysis of the results

The study report states in the introduction that the evaluation of the product's efficacy was based on a comparison of alcohol levels at each evaluation time between Day 0 and Day 3.
In reality, the calculations were made based on the differences between measurements at different times for the same patient:
For Group 1:

- $t_{30a} - t_{30}$
- $t_{45} - t_{30}$
- $t_{45} - t_{30a}$

For Group 2:

- $t_{45} - t_{30}$

- $t_{60} - t_{30}$

The values of these differences were compared between Day 0 and Day 3 (or Day 6 for Group 1). From the results of these comparisons, the following conclusions were drawn:

- For Group 1, the increase in alcohol level in the exhaled air was significantly lower with the product than that observed with the placebo.
- For Group 2, there was a significant decrease in the alcohol level in the exhaled air with the product 45 minutes after it was administered, compared with the decrease observed after administration of the same quantity of alcohol alone.

ANSES deems this method of statistical analysis inappropriate. In fact, the statistical analysis disregards the fact that observations made repeatedly on the same subjects are not independent, and it does not take into account the relationships between them, whether with regard to repetitions over time, treatment repetitions or interactions.
In addition, the complex kinetics of alcohol in the body complicates the interpretation of the variations in these differences.

4.3.3. Study results

In light of the lack of pertinence of a comparison of the differences in measurements between Day 0 and Day 3, ANSES considers it necessary to refer to the mean values and the standard deviations of each measurement to analyse the study results. These values (g/L) are summarised in Tables 1 and 2.

Table 1. Alcohol level in exhaled air (g/L of blood) in Group 1 (n=12 subjects)

	Day 0 (alcohol + placebo)	Day 3 (alcohol + product)
	Mean ± standard error	Mean ± standard error
t_{30}	0.53 ± 0.02	0.58 ± 0.02
t_{30a}	0.89 ± 0.05	0.82 ± 0.03
t_{45}	0.84 ± 0.04	0.78 ± 0.03

Table 2. Alcohol level in exhaled air (g/L of blood) in Group 2 (n=43 subjects)

	Day 0 (alcohol alone)	Day 3 (alcohol + product)
	Mean ± standard error	Mean ± standard error
t_{30}	1.24 ± 0.04	1.27 ± 0.05
t_{45}	1.11 ± 0.03	1.12 ± 0.04
t_{60}	1.08 ± 0.04	1.00 ± 0.04

The above results show that the mean levels of alcohol in the exhaled air at the different times between Day 0 and Day 3 were similar. Also, if a difference were to be shown as statistically significant by an appropriate test, it would be of no biological significance since it was less than 0.1 g/L in all cases for high alcohol levels (between 0.8 and 1.20 g/L), and no differences were seen at the earlier times (t_{30} for Group 1; t_{30} and t_{45} for Group 2). Finally, there is considerable dispersion of the alcohol levels between the subjects: with the same quantity of ingested alcohol, there was a one- to three-fold variation in alcohol levels.

In the behavioural part of the study, the results indicate that the behaviour of the subjects in Group 1 did not improve with use of the product. In Group 2 however, improvements in attention, alertness, memory recall and responsiveness were observed, while the blood alcohol levels remained identical whether or not the product was administered.
ANSES believes that the choice of the evaluation method, which is not suited to the intended aim, explains these contradictory results. In particular, the rating methodology was not specified and there was no prior objective testing to assess the relevance of the evaluation of cognitive functions, which is particularly important since this evaluation is highly complex, especially with regard to memory. ANSES thus considers that no conclusions can be drawn from this behavioural study.

Finally, ANSES points out that a previous study had been conducted with the beverage proposed by the applicant (Pavlic *et al*., 2007). This was a double-blind, placebo-controlled study conducted on 30 healthy volunteers that had consumed alcohol *ad libitum* over two hours (1.06 ± 0.24 g/kg bw on average), followed by 25 cL of the product 15 minutes afterwards, or the same quantity of alcohol followed by a placebo.
Alcohol levels in the blood and in the exhaled air were measured every 30 minutes for five hours.
The primary endpoint was the comparison of the rate of alcohol elimination and the blood alcohol levels at each evaluation point, both with the product and with the placebo. A complete statistical analysis enabled in particular a comparison of the blood alcohol levels between both groups at each evaluation time.
The results show a significant statistical difference ($p < 0.0001$) between the blood alcohol levels with the product and those with the placebo (0.077 g/L on average, i.e. 10.3% compared to the placebo). On the other hand, the alcohol elimination rate did not change.
These results show that the reduction of the observed blood alcohol level, around 10%, is too low to be of biological significance or to reduce the consequences, particularly those that are behavioural, induced by the alcohol. Furthermore, the gradient of alcohol elimination did not change, thus the role of the beverage on alcohol metabolism could not be confirmed. There appears to be another non-specific effect present. The authors moreover suggest an effect that could be reproduced through the use of other caloric beverages or foods.

5. CONCLUSION

Concerning the bibliographic data, ANSES emphasises that the studies on the effects of fructose or ascorbic acid were conducted with very diverse experimental protocols and often in a limited numbers of healthy volunteer subjects or alcohol-dependent patients. The methodological weaknesses of these studies do not enable conclusions to be drawn as to the effects of these nutrients on the elimination of ethanol.

Concerning the study provided by the applicant, ANSES emphasises that the composition of the product used in the study was not specified. It is therefore not possible to guarantee the transposition of the results to the marketed product. Furthermore, the open label and non-crossover design of the trial could possibly bias the results. The statistical analysis used was not appropriate for the aim of the study, and the protocol was unsuited to the kinetics of alcohol elimination. In addition, the rating method for the cognitive criteria in the behavioural part of the study was not specified.
ANSES therefore considers that a claim regarding the reduction of blood alcohol levels for the product is not acceptable.

The decrease in alcohol levels related to consumption of the product, as reported in the study (without prejudice to its demonstration), has a high level of inter-individual variability and is too small to have biological significance and reduce the consequences, particularly behavioural, induced by alcohol.

ANSES indicates that the risks associated with alcohol consumption are totally eliminated only for blood alcohol levels equal to zero. Within the framework of risk prevention related to alcohol consumption, a claim mentioning a reduction in blood alcohol levels presents a risk that is likely to give consumers a false sense of security.

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The Director General

Marc MORTUREUX

KEYWORDS

ALCOHOL, ETHANOL, CLAIM, FRUCTOSE, ASCORBIC ACID

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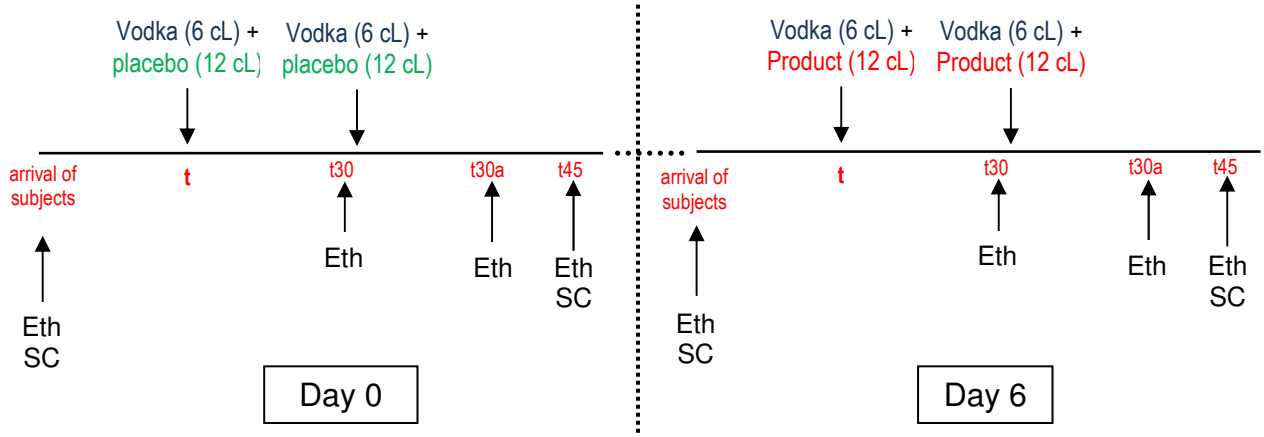
ANNEXES

1. Freudenberg Table (Barrucand, 1988)

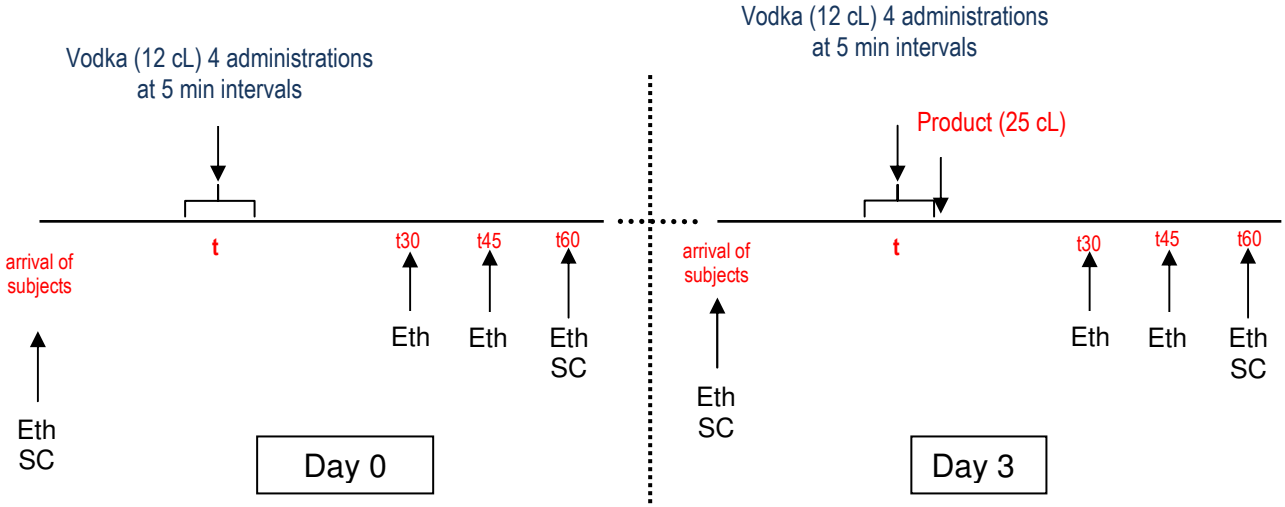
BLOOD ALCOHOL LEVELS (in g/L)	Coefficient of accident endangerment		
	Fatal	Bodily	Material
0.0	1.00	1.00	1.00
0.1	1.20	1.16	1.07
0.2	1.45	1.35	1.15
0.3	1.75	1.57	1.24
0.4	2.10	1.83	1.35
0.5	2.53	2.12	1.43
0.6	3.05	2.47	1.53
0.7	3.67	2.87	1.65
0.8	4.42	3.33	1.77
0.9	5.32	3.87	1.90
1.0	6.40	4.50	2.09
1.1	7.71	5.23	2.19
1.2	9.29	6.08	2.35
1.3	11.18	7.07	2.52
1.4	13.46	8.21	2.71
1.5	16.21	9.55	2.91

2. Implementation of the study provided by the applicant

Group 1 (12 subjects)



Group 2 (43 subjects)



Eth: Breathalyser test
CS: clinical score