European Food Safety Authority

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SCIENTIFIC OPINION

Reconsideration of the temporary ADI and refined exposure assessment for Sunset Yellow FCF (E 110)[1]

EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

The Panel on Food Additives and Nutrient Sources added to Food (ANS Panel) has previously provided a scientific opinion re-evaluating the safety of Sunset Yellow FCF (E 110) as a food additive in the EU and establishing a temporary acceptable daily intake (ADI) of 1 mg/kg bw/day (EFSA ANS Panel, 2009). Following a request by the European Commission, the ANS Panel was asked to assess newly submitted data from a study conducted as a result of the recommendations contained in the 2009 opinion. In addition, EFSA was requested to carry out the refined exposure assessment of Sunset Yellow FCF. The new information assessed comprised an evaluation of the 28-day study report, the data considered by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in its latest evaluation from 2011, and any additional toxicological information that had become available since the completion of the previous evaluation by the ANS Panel. The ANS Panel has considered that the newly submitted data from the 28-day study and the overall available toxicological database on Sunset Yellow FCF provides a basis to revise the established temporary ADI and concluded that, based on the NOAEL of 375 mg/kg bw/day from the long-term feeding study in rats and an uncertainty factor of 100, a new ADI for Sunset Yellow FCF of 4 mg/kg bw/day can be established, in agreement with the latest evaluation by JECFA. Exposure estimates for Sunset Yellow FCF based both on the currently authorised MPLs and reported use levels provided are well below the new ADI of 4 mg/kg bw/day for all population groups. Overall, the Panel concluded that, using data provided by the food industry and Member States, the reported uses and use levels of Sunset Yellow FCF (E 110) would not be of safety concern.

KEY WORDS

Sunset Yellow FCF, E 110, 28-day study, ADI, refined dietary exposure, food colours

[1] On request from the European Commission, Question No EFSA-Q-2013-00248, adopted on 26 June 2014.

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SUMMARY

In 2009 the EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS Panel) has adopted a scientific opinion on the re-evaluation of Sunset Yellow FCF (E 110) as a food additive in the EU. In its opinion, the ANS Panel established a temporary acceptable daily intake (tADI) of 1 mg/kg bw/day and requested a 28-day study with Sunset Yellow FCF to be performed in accordance with OECD guidelines and with well-defined material, in order to clarify the histopathological changes in the testes and the changes in the blood lipid profile observed by Mathur el al. (2005a, 2005b) in rats, after 90-day dietary exposure to Sunset Yellow FCF at dose levels equivalent to 250 and 1 500 mg/kg bw/day.

Following a request from the European Commission, the ANS Panel was asked to deliver a scientific opinion on the data generated from a 28-day study conducted as a result of the recommendations contained in the 2009 opinion and whether, on the grounds of these new data, the ADI should be reconsidered.

Furthermore, following the conclusions of the 2009 opinion as regards exposure to Sunset Yellow FCF (E 110), EFSA was requested to carry out a refined exposure assessment for this food additive. In that opinion, the ANS Panel had evaluated the exposure to Sunset Yellow FCF (E 110) on the basis of the uses and use levels authorised in the legislation and the reported use levels as provided by industry, and concluded that at the maximum reported levels of use of Sunset Yellow FCF, refined intake estimates were generally below the temporary ADI of 1 mg/kg bw/day. However, in 1- to 10-year old children, the mean and the high percentiles of exposure could be higher than this temporary ADI, at the upper end of the range.

The ANS Panel noted that since the publication of its scientific opinion on the re-evaluation of Sunset Yellow FCF for use as a food additive in 2009, an updated evaluation has been completed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2011 (JECFA, 2011). In its latest evaluation, JECFA concluded that the ADI for Sunset Yellow FCF should be increased from 2.5 mg/kg bw/day to 4 mg/kg bw/day. Thus, the ANS Panel considered that, in order to fulfil the current mandate, the latest evaluation performed by JECFA in 2011 was also to be taken into account for the setting of an ADI for this food colour, alongside any other relevant publications that might have become available since the publication of the previous scientific opinion.

The ANS Panel considered the results from a dietary 28-day study in male Hsd:SD® rats performed by Product Safety Labs (2012) using levels of Sunset Yellow FCF up to 18 000 mg/kg diet (equivalent to 1 475 mg/kg bw/day), and performed according to the current OECD guidelines, and concluded that the findings reported by Mathur et al. (2005a, 2005b) on lipid profile and testes histopathology were not confirmed. The Panel agreed with the authors of the 28-day study that the NOAEL of this study was 18 000 mg/kg diet (equivalent to 1 475 mg/kg bw/day), the highest dose level tested. The Panel noted that the material tested in this 28-day study met the EU specifications for Sunset Yellow FCF as a food additive. The Panel, based on the data described in its 2009 opinion and the results from this new 28-day study, concluded that the findings of the Mathur studies (2005a, 2005b) should be disregarded for the risk assessment of Sunset Yellow FCF.

The ANS Panel also evaluated one unpublished long-term feeding study in mice and two studies in rats provided by the United States Food and Drug Administration (FDA), which had also been considered by JECFA in its latest evaluation from 2011. In the light of the data from these long-term feeding studies, the ANS Panel concluded that no carcinogenic potential of Sunset Yellow FCF was observed in mice and rats. Based on the occurrence of the adverse effect on pup body weight gain, observed during the last part of the lactation in a long-term rat study in the group fed 1.5 % FD&C Yellow No. 6 (Sunset Yellow FCF) in the diet, and described in the full reports provided by the FDA, the Panel agreed with JECFA that the NOAEL for this study was 0.75 % (equivalent to 375 mg/kg bw/day). The Panel considered that, this NOAEL being obtained from a long-term study including an

in utero phase, an uncertainty factor of 100 can be applied for the derivation of a new ADI of 4 mg/kg bw/day.

Lastly, the results of an extensive literature search performed on three electronic databases (PubMed, Web of Science and Toxnet) and covering the time span between approximately one year before the adoption of the opinion on the re-evaluation of Sunset Yellow FCF (i.e. from 1 November 2008) until 31 December 2013, aiming to retrieve any additional relevant toxicological data, was reviewed by the ANS Panel.

The safety of Sunset Yellow FCF, with particular respect to the data on its metabolism, genotoxicity and carcinogenicity, had already been reviewed by the ANS Panel in the context of the recent assessment of Allura Red AC and other structurally related sulphonated mono azo dyes (EFSA ANS Panel, 2013). The additional extensive literature search did not reveal any new data in addition to those already considered in this statement.

A study was carried out to investigate the effect of oral administration of Amaranth, Sunset Yellow FCF and Curcumin on immunological responses (Hashem et al., 2010). Sunset Yellow FCF (315 mg/kg bw/day) was administered by gavage to female Sprague Dawley albino rats for 4 weeks. The authors stated that Sunset Yellow used at dose of 315 mg/kg bw/day exerted a depressing effect on the cellular, but not humoral, immune response. The Panel noted that this study was conducted with locally sourced uncharacterised material of unknown purity and did not consider this study suitable for risk assessment.

Oestrogenic activity of Sunset Yellow FCF was demonstrated in an *in vitro* model system (Axon et al., 2012). According to EFSA's Scientific Opinion on the hazard assessment of endocrine disruptors (EFSA SC, 2013) *"the fact that a substance in an in vitro assay is binding to an endocrine receptor, then interfering with the intracellular messenger system connecting receptor to target or resulting in an endocrine-related response in a target cell, must be taken as strong indication for endocrine activity. If a suitable animal model provides further indication for an endocrine-related adverse effect, this substance should be considered an endocrine disruptor"*. However, in long-term studies including an *in utero* phase in mice and rats, no effects on endocrine and reproductive organs were observed. Therefore, the results of this *in vitro* study were not further considered in the risk assessment.

In conclusion, the newly submitted data from the 28-day toxicity study and the overall available toxicological database on Sunset Yellow, including long-term studies, provides a basis to revise the established temporary ADI. Based on the NOAEL of 375 mg/kg bw/day from the long-term feeding study in rats and an uncertainty factor of 100, a new ADI for Sunset Yellow FCF of 4 mg/kg bw/day was established.

A refined exposure assessment for Sunset Yellow FCF (E 110) has been performed taking into consideration the Maximum Permitted Levels (MPLs) of use currently authorised in Annex II of Regulation (EC) No 1333/2008.

Overall, exposure estimates for Sunset Yellow FCF (E 110) based on the currently authorised MPLs of use in foods are well below the new ADI of 4 mg/kg bw/day established by the ANS Panel, for all population groups. This is due both to the fact that MPLs for Sunset Yellow FCF were largely decreased, following the amendment of the legislation in 2013, and to a more refined exposure assessment being performed, taking into account the restrictions/exceptions listed in Annex II of Regulation (EC) No 1333/2008 and the use of the EFSA Comprehensive Database (FoodEx) system.

It should be noted that in 2012, further to the amendment of Annex II of Regulation (EC) No 1333/2008 as regards the conditions of use and the use levels for Sunset Yellow FCF (E 110) , MPLs were either withdrawn or decreased by a factor of 2 to 30. Updated information on the actual use levels of Sunset Yellow FCF in foods was made available by the industry for few of the food categories in which this food additive is authorised. In addition, concentration data on Sunset Yellow

FCF in foods were provided by Member States. These data were in their majority collected before June 2013. Nevertheless, in the absence of more recent data, these data were also considered for the refined exposure assessment scenario, provided that the values were below the currently authorised MPLs of use of Sunset Yellow FCF.

The Panel noted that the results of the present exposure estimates for Sunset Yellow FCF based both on the currently authorised MPLs and reported use levels are well below the new ADI of 4 mg/kg bw/day for all population groups. The exposure results are much lower compared to the ones from the exposure assessment performed by the ANS Panel in 2009 (EFSA ANS Panel, 2009) for all population groups. For children and toddlers, the present results are of the same magnitude when compared with the exposure estimates obtained in the refined exposure assessment of Sunset Yellow FCF (E 110) performed by EFSA in 2011.

Overall, the Panel concluded that using data provided by the food industry and Member states, the reported uses and use levels of Sunset Yellow FCF (E 110) would not be of safety concern.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

The European Food Safety Authority (EFSA) has re-evaluated the safety of Sunset Yellow FCF (E 110) as a food additive in 2009 (EFSA ANS Panel, 2009).

EFSA decided to reduce the ADI, by an extra uncertainty factor of 2.5, to 1 mg/kg bw/day and to make the ADI temporary for 2 years. Furthermore, it was stressed that within that period, clarification of the effects of Sunset Yellow FCF on the testis, sperm morphology and sperm mobility should be provided, based on a 28-day study performed according to the updated OECD test guideline 407.

The study in question has now been submitted by the International Association of Color Manufacturers.

The European Commission asks EFSA to evaluate this new information and possibly reconsider the temporary ADI established for Sunset Yellow FCF.

The above request for evaluation of new toxicological data on Sunset Yellow FCF (E 110) has been combined with a previous request to EFSA to provide a refined exposure assessment for twelve food colours, including Sunset Yellow FCF, which were already re-evaluated by the ANS Panel and for which a possible exceedance of the ADI was shown.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Article 29 (1) (a) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority to provide a scientific opinion as regards the clarification of the effects of Sunset Yellow FCF on the testis, sperm morphology and sperm mobility and to reconsider the temporary ADI based on this clarification.

In addition, the European Food Safety Authority is to provide a refined exposure assessment for Sunset Yellow FCF (E 110) taking into account the restrictions/exceptions listed in Annex II of Regulation (EC) No 1333/2008, especially in the case of main contributors. In order to provide a refined exposure assessment, EFSA is requested to use the EFSA Comprehensive Food Consumption Database (FoodEx) system, excluding the non-relevant food subgroups from the intake calculations.

INTERPRETATION OF TERMS OF REFERENCE

The ANS Panel noted that since the publication of its scientific opinion on the re-evaluation of Sunset Yellow FCF for use as a food additive in 2009, an updated evaluation has been completed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2011 (JECFA, 2011). In its latest evaluation, JECFA concluded that the ADI for Sunset Yellow FCF should be increased from 2.5 mg/kg bw/day to 4 mg/kg bw/day. Thus, the ANS Panel considered that, in order to fulfil the current mandate, the latest evaluation performed by JECFA in 2011 should also be taken into account for setting an ADI for this food colour, alongside any other relevant publications that might have become available since the publication of the previous scientific opinion.

EVALUATION

1. Introduction

Sunset Yellow FCF (E 110)[4] is an azo dye authorised as a food additive in the EU and previously evaluated by JECFA (JECFA, 1982) and the Scientific Committee for Food (SCF) in 1983 (SCF, 1984). Both committees, at the time, established an ADI of 0-2.5 mg/kg bw/day.

The EFSA ANS Panel has re-evaluated the safety of Sunset Yellow FCF (E 110) as a food additive in 2009 (EFSA ANS Panel, 2009). The Panel decided to reduce the ADI to 1 mg/kg bw/day, by applying an extra uncertainty factor of 2.5, and to make the ADI temporary for 2 years. This decision was based on the effects observed in the testis of rats in a study where Sunset Yellow of unknown purity, bought on the local market in India, was used as the testing material (Mathur, 2005a). The ANS Panel stressed that within a period of 2 years, clarification of the effects of Sunset Yellow FCF on the testis, sperm morphology and sperm mobility should be provided, based on a 28-day study performed according to the updated OECD test guideline 407. In sub-chronic and chronic studies, described in the former evaluations by JECFA and the SCF, no effects on testes or other reproductive effects were described. For that reason, the ANS Panel in its 2009 opinion decided to ask for a 28-day toxicity study with well-defined material.

Following a request by the European Commission, asking EFSA for a reconsideration of the temporary ADI of Sunset Yellow FCF (E 110) based on a newly submitted 28-day study in rats (Products Safety Labs, 2012, unpublished), the ANS Panel evaluated the new data provided and reconsidered the temporary ADI of 1.0 mg/kg bw/day established by the ANS Panel in 2009 (EFSA ANS Panel, 2009).

In addition, the ANS Panel noted that in 2011 JECFA withdrew the previously set ADI for Sunset Yellow FCF, and established a new ADI of 0-4 mg/kg bw/day (JECFA, 2011). This latest JECFA evaluation encompassed previously reviewed data, published information that had become available since Sunset Yellow FCF was last considered by JECFA, and a comprehensive review of one unpublished long-term feeding study in mice and two studies in rats, provided by the United States Food and Drug Administration (FDA).

Additionally, in reconsidering the previously established temporary ADI, the ANS Panel evaluated other relevant publications that have become available since the publication of its previous scientific opinion and were identified through an ongoing procurement contract for extensive literature searches on food additives, previously evaluated by the ANS Panel.

Furthermore, following the conclusions of the 2009 opinion as regards anticipated dietary exposure to Sunset Yellow FCF (E 110), EFSA was requested to carry out a refined exposure assessment for this food additive. In that opinion, the ANS Panel had evaluated the exposure to Sunset Yellow FCF (E 110) on the basis of the uses and use levels authorised in the legislation and the reported use levels as provided by industry, and concluded that at the maximum reported levels of use of Sunset Yellow FCF, refined intake estimates were generally below the temporary ADI of 1 mg/kg bw/day. However, in 1- to 10-year old children, the mean and the high percentiles of exposure could be higher than this temporary ADI, at the upper end of the range.

The aim of the revised exposure assessment is to provide updated exposure estimates for Sunset Yellow FCF, from its use as a food colour, using the EFSA Comprehensive European Food Consumption Database (Comprehensive Database) and the FoodEx classification system and taking into consideration the restrictions/exceptions listed in Annex II of Regulation (EC) No 1333/2008.

[4] The food colour Sunset Yellow FCF (E 110), with CAS Registry Number No. 2783-94-0 is also known as FD&C Yellow No. 6 (or FD&C Yellow # 6). In this opinion both terminologies have been used synonymously.

Through a call[5] for concentration and usage data on Sunset Yellow FCF (E 110) in foods, launched by EFSA in March 2013, new data were made available from Member States (MS) and by the industry.

2. Evaluation of new toxicological data

2.1. 28-day dietary study in male rats

The ANS Panel was provided with data from a 28-day dietary study in male rats conducted by Product Safety Labs (2012, unpublished).

The study by Product Safety Labs, was performed under Good Laboratory Practice (GLP) and a certificate of analysis of the test substance, FD&C Yellow No. 6/Sunset Yellow FCF was included in the report. As proposed by the ANS Panel (EFSA ANS Panel, 2009), histopathological examination and sperm analysis were performed after dietary exposure of male rats for 28 days following OECD test guideline 407 (OECD, 2008).

Product Safety Labs (2012, unpublished) performed a 28-day dietary study in male Hsd:SD® rats (n=10/group) to determine the potential of FD&C Yellow No. 6/Sunset Yellow FCF to produce toxicity. Dietary levels of 0 mg/kg, basal diet, 6 000 mg/kg, 12 000 mg/kg, 18 000 mg/kg were tested (equivalent to 0, 490, 944 and 1 475 mg/kg bw/day, respectively). The diets were provided *ad libitum*. Homogeneity, stability and concentration of the test diets were verified. The animals were observed for signs of toxicity and behavioural changes at least once daily during the study, and weekly for a battery of detailed clinical observations. Body weights were recorded prior to test initiation (day 0), and approximately weekly thereafter, and just prior to sacrifice. Individual food consumption was also recorded to coincide with body weight measurements. Blood was sampled from all animals for haematology and clinical chemistry analysis and prior to necropsy for coagulation assessments. Necropsies were performed on all animals in the study, and selected organs and tissues from all animals were preserved. Microscopic evaluation was performed on organs and tissues of animals of the control and the 18 000 mg/kg groups. In addition, gross lesions of potential toxicological significance, noted at the time of terminal sacrifice, were also examined microscopically.

There were no mortalities during the study. In-life clinical observations included orange scrotum staining and orange/red cage staining for all animals of the test dose groups; red nasal discharge for one animal in the 6 000 mg/kg group, and soft faeces for one animal each in the 6 000 and 12 000 mg/kg groups, and 6 animals fed 18 000 mg/kg. Two control animals exhibited black/red nasal discharge. There were no test substance-related effects on body weight, body weight gain, food consumption or food efficiency. White blood cell concentration and absolute basophil concentration was decreased in males fed 18 000 mg/kg. No statistically significant differences in coagulation parameters were observed. Cholesterol concentration was decreased in males fed 6 000 and 18 000 mg/kg, albumin was increased in males fed 12 000 mg/kg, inorganic phosphorus was decreased in males fed 18 000 mg/kg, sodium concentration was decreased in males fed 18 000 mg/kg. Urine pH was decreased in males fed 12 000 and 18 000 mg/kg, urobilogen concentration was increased in males fed 12 000 mg/kg. The authors stated that these findings, which were not accompanied by clinical and histopathological changes, were considered non-adverse and toxicologically insignificant. Similarly, at scheduled sacrifice, there were no macroscopical or histological findings related to the test substance, FD&C Yellow No. 6/Sunset Yellow FCF. At macroscopic examination, for each of the control group and the group fed 12 000 mg/kg, one male showed left epididymal cysts, which was confirmed microscopically as a sperm granuloma. The statistically significant increases in testes-to-brain weight ratios observed in animals of the groups fed 12 000 and 18 000 mg/kg were not accompanied by histopathological findings in the 18 000 mg/kg group. Absolute testes weight and testes-to-body weight of these groups were not statistically significantly increased. The sperm analysis (sperm motility, epididymal sperm count, homogenization resistant spermatid count, or sperm morphology) showed no dose-related adverse effects. Therefore, the authors concluded that under the

[5] Call for food additives usage level and/or concentration data in food and beverages intended for human consumption. Published: 27 March 2013. http://www.efsa.europa.eu/en/data/call/130327.htm

conditions of this study and based on the endpoints evaluated, the No-Adverse-Effect Level (NOAEL) of FD&C Yellow No. 6/Sunset Yellow FCF in the diet of male rats is 18 000 mg/kg diet (equivalent to 1 475 mg/kg bw/day), the highest dose level tested. The Panel agreed with this conclusion.

2.2. Latest evaluation by JECFA (2011)

The ANS Panel noted that in 2011 JECFA withdrew the previously set ADI for Sunset Yellow FCF, and established a new ADI of 0-4 mg/kg bw/day (JECFA, 2011). This latest evaluation performed by JECFA encompassed previously reviewed data, published information that had become available since Sunset Yellow FCF was last considered by the Committee and a comprehensive review of one unpublished long-term feeding study in mice and two in rats, provided by the United States Food and Drug Administration (FDA). Detailed summaries of these studies are also reported in the FDA Final Rule on the permanent listing of FD&C Yellow No 6 for use generally in food drugs and cosmetics[6].

2.2.1. Summary of the unpublished long-term feeding studies reviewed by FDA and used to determine the ADI of 4 mg/kg bw/day by JECFA

The full study reports for the long-term feeding studies (one in mice and two studies in rats which were mentioned in the 2011 JECFA evaluation) were made available to the ANS Panel.

Mice

The final study report, dated 31 December 1982, and obtained from FDA, refers to Project No. 77-1779 "A long-term oral carcinogenicity study of FD&C Yellow #6 in mice" by Bio/dynamics Inc. The abstract states the following: "This study, conducted for the Certified Color Manufacturers Association (CCMA) was designed to evaluate the carcinogenicity of FD&C Yellow #6 and to meet requirements established by the U.S. FDA, Bureau of Foods, for long-term feeding studies in mice".

FD&C Yellow No. 6 was administered continuously in the diet to 600 Charles River CD-1 mice (60/sex/group) at dose levels of 0 % (control IA), 0 % (control IB), 0.5 %, 1.5 % and 5.0 % for approximately 20 and 23 months (males and females, respectively). Ten animals/sex/group were randomly selected for haematology evaluations at 3, 6, 12 and 18 months. All surviving males were sacrificed in Month 20 and all surviving females in Month 23.

Mortality was comparable for the control and high-dose females, although mortality occurred earlier in the high-dose females, i.e. 50 % mortality occurred in Month 17 for the high-dose females versus Month 18 or 19 for the control females. In males, mortality was higher in the high-dose group ($p < 0.01$) and occurred earlier, i.e. 50 % mortality occurred in Month 16 for the high-dose males versus Month 18 or 19 for the control males. Mean body weights for the high-dose males and females were consistently lower than those of the controls throughout the study. Differences from controls at the end of the study were -10 % and -9 % for the high-dose males and females, respectively. Food consumption was consistently increased for the mid- and high-dose males relative to controls, while values for the low-dose males were only slightly increased. No treatment-related effect was apparent on mortality or body weight data for the low- and mid-dose animals, food consumption of treated females, or haematologic parameters for all treated groups. Following the first year of the study, an increased incidence of ocular opacities was noted in the high-dose females. At the same time in the study, in males, the incidence was highest in one of the control groups. As the incidence in the high-dose females and control males was comparable, this observation was considered of equivocal significance by the authors of the study. The Panel agreed with this conclusion. After the first year, an increased incidence of abdominal distension was observed in all groups, including controls. Complete histopathological examination of all preserved organs and tissues (including reproductive organs), tissues masses and other gross changes was done. The evaluation of these tissues revealed a variety of neoplastic and non-neoplastic changes. These histopathological changes were considered unrelated to the dietary administration of FD&C Yellow No. 6. Statistical analysis of neoplasm data indicated no

[6] Federal Register, Volume 51, No 223, November 19, 1986. P. 41765-41783. 21 CFR Parts 74, 81, 82, and 201 [Docket No 86C-0192].

increase in the incidence, nor decreased time to onset in the treated groups. The gross and microscopical examination revealed no adverse histopathological changes that could be attributed to treatment with FD&C Yellow No. 6.

Rats

Two long-term feeding studies with *in utero* exposure to FD&C Yellow No. 6 were carried out in Charles River Albino (CD)® rats.

The final study report, dated 31 December 1982, and obtained from FDA, refers to Project No. 77-1778 "A long-term oral carcinogenicity study of FD&C Yellow #6 in rats" by Bio/dynamics Inc. The abstract states the following: "This study, conducted for the Certified Color Manufacturers Association (CCMA) was designed to evaluate the toxicity and carcinogenicity of FD&C Yellow #6 and to meet requirements established by the U.S. FDA, Bureau of Foods, for long-term feeding studies with exposure beginning *in utero*".

FD&C Yellow No. 6 was administered continuously in the diet to 600 Charles River Albino rats (60/sex/group) at dose levels of 0 % (control IA), 0 % (control IB), 0.75 %, 1.5 % and 3.0 % for approximately two months prior to mating. Following the reproductive phase, a maximum of 2 animals/sex/litter within each group, were randomly selected to populate the long-term segment (F_1) of the study. Dietary administration continued at the same dose levels for 700 rats (70/sex/group) for a period of approximately 30 months for the males and 29 months for the females. Ten animals/sex/group were randomly selected for clinical laboratory examinations at 3, 6, 12, 18 and 24 months. Ophthalmoscopic examinations were performed on all animals following receipt (F_0), after selection for the long-term segment and at the 3, 6, 12, 18 and 24 months interval (F_1). An interim necropsy of 10 rats/sex/group was performed at 12 months. All surviving male animals (9) were sacrificed in Month 30 and the surviving females (9) in Month 29.

During the F_0 generation (premating period), no treatment-related effect on mortality was noted. However, body weights were lower and food consumption was increased in a dose-related manner in the mid- and high-dose males. Mean pup weight at birth was greater in the high-dose group than in controls. However, pup survival was reduced early during lactation and pup weight gain was reduced throughout lactation, which resulted in the lowest pup weight of this group at day 21 of lactation. Mean pup weight was also reduced for the mid-dose group at the end of lactation. No other effects on reproduction parameters were noted. During the F_1 generation, mortality was higher in the high-dose females than in controls. However, the difference from controls was not statistically significant. Body weights for the mid- and high-dose males and females were lower than controls at the initiation of the F_1 part of the study. Thereafter, body weights for all treated groups were generally comparable to, or greater than controls throughout most of the study, with the exception that at the end of the study body weights of the mid-dose males and high-dose animals of both sexes were lower than that of controls (< -10 %). Food consumption was increased for all treated females and males during the first month (males) and first three months (females) of the F_1 generation. Thereafter, increased food consumption was noted in the high-dose males and females, and sporadically in the mid-dose females. Higher blood urea nitrogen concentrations were noted in the high-dose females in months 18 and 24: differences from controls were statistically significant. Slight elevations in serum glutamic oxaloacetic transaminases noted in the mid- and high-dose males in months 18 and 24 were considered of equivocal toxicological significance.

At sacrifice after 12 months, organ weight data for the treated animals were comparable to those for controls. At the terminal sacrifice, the mean body weight of the high-dose females was markedly lower than that of controls, while the absolute and relative (to body weight) weights of the kidneys were elevated (the latter being statistically significant). The absolute and relative kidney weights for the low- and mid-dose females and mid- and high-dose males were also slightly elevated. No treatment-related effects were apparent from general physical observations, ophthalmology or haematology data. Macroscopical examination revealed yellow to orange discolouration of the

gastrointestinal tract in animals of the treated groups. An increased incidence of adrenal masses was noted in the low- and high-dose males. Histopathological examination of tissues from all control and high-dose rats revealed no carcinogenic effect in male rats that could be attributed to treatment with FD&C Yellow No. 6. In females of the high-dose group, an increased incidence of adrenal medullary tumours (phaeochromocytomas) was observed. The increase was statistically significant by the Fischer Exact test. The FDA scientists have concluded, and the Panel agreed with that conclusion, that the higher incidence of rats with phaeochromocytomas in the high-dose female group is not related to treatment with FD&C Yellow No. 6 for the following reasons: 1. the small increase in the number of treated animals with a type of tumour of a spontaneous high and variable incidence; 2. the lack of any effect on the latency period; 3. the absence of a dose-response relationship between the incidence and severity of the medullary lesions (phaeochromocytomas and hyperplasias); 4. the lack of a treatment-related effect on medullary adrenal lesions in male rats; 5. the lack of similar effects in male or female rats in any of the other rat studies conducted with FD&C Yellow No. 6.

The other final study report, dated 31 December 1982, and obtained from FDA, refers to Project No. 78-2211 "A long-term oral toxicity/carcinogenicity study of 5.0 % FD&C Yellow #6 in rats*"* by Bio/dynamics Inc. The abstract states the following: "This study, conducted for the Certified Color Manufacturers Association (CCMA) was designed to evaluate the potential toxicity and carcinogenicity of FD&C Yellow #6 and to meet requirements established by the U.S. FDA, Bureau of Foods, for long-term feeding studies with exposure beginning *in utero"*.

FD&C Yellow No. 6 was administered continuously in the diet to 240 Charles River Albino rats (60/sex/group) at dose levels of 0.0 % and 5.0 % for approximately two months prior to mating. Following the reproductive phase, a maximum of 2 animals/sex/litter within each group were randomly selected to populate the long-term segment (F_1) of the study. Dietary administration continued at the same dose levels for 280 rats (70/sex/group) for a period of approximately 26 and 28 months, for males and females respectively. Ten animals/sex/group were randomly selected for clinical laboratory analyses at 3, 6, 12, 18 and 24 months (F_1). Ophthalmoscopic examinations were performed on all animals following receipt (F_0), after selection for the long-term segment and at the 3, 6, 12, 18 and 24 months interval (F_1). An interim necropsy of 10/sex/group was performed at 12 months. The study was terminated in Month 26 and Month 28, for male and female rats, respectively.

During the F_0 generation (premating period), no treatment-related effect on mortality was noted. However, body weights of the treated males were lower than those of controls, while food consumption was increased for the treated males and females. Pup survival was reduced for the treated group during days 0-14 of lactation and during the post-weaning period, while mean pup weight was lower than that of controls at day 21 of lactation. No other effects on reproduction parameters were noted. During the F_1 generation, mortality of the treated males and females was slightly higher than that of controls; differences from controls were statistically significant for the males only. Body weights of the treated males and females were lower than that of controls at the initiation of the F_1 part of the study and remained lower throughout the remainder of the study. Differences from controls were generally statistically significant for the males, but less frequently for the females. At the end of the study, differences from control weights were -15 % and -17 % for the treated males and females, respectively. Food consumption was statistically significantly increased for the treated animals throughout the study. Slight to statistically significant decrease in the mean haemoglobin concentration, haematocrit and erythrocyte counts were noted in the treated animals at Months 3 and 6. However, as values for these parameters were comparable to or higher than those of controls at subsequent intervals, these difference were not considered to be of toxicological significance.

At sacrifice after 12 months, slight but not statistically significant increases in the mean absolute and relative (to body weight) kidney weights were noted in the treated females. At the terminal sacrifice, the absolute and relative weights of the thyroids were elevated in the treated males and females. In the females, the absolute and relative kidney weight was slightly, but not statistically significantly increased. Slight increases in relative liver and testes weights were also noted in the treated animals. No treatment-related effects were apparent from general physical observation or ophthalmology data.

Macroscopical examination revealed yellow/orange intestinal discolouration and splenic nodules/mass(es) in treated male animals. Histopathological evaluation of all tissues of the controls and treatment group revealed an increased incidence of renal tubular cell adenomas in females (5/70 versus 0/70 in the control group). Other tissue alterations noted occurred with comparable incidence in control and treated animals, and were not considered related to the administration of FD&C Yellow No. 6.

An *ad hoc* Panel of Experts constituted a National Toxicology Program (NTP) Peer Review Panel which reviewed the slides of the kidney lesions from the female rats of the 5 % FD&C Yellow No. 6 group and their controls. The NTP Peer Review Panel concluded that *"the weight of evidence of all the studies does not suggest that FD&C Yellow No. 6 is a renal carcinogen"*. The main reasons that led the NTP Peer Review Panel to this conclusion are: 1. the acknowledged debatable nature of the small renal proliferative lesions variously categorised by different pathologists as representing nodular hyperplasia, adenomatous hyperplasia or benign renal tubular adenomas; 2. the lack of concurrence as to whether lesions were hyperplastic or benign; 3. the absence of any definitive malignant renal cortical tubular neoplasms in the treated rats; 4. the absence of any type of renal tubular proliferative response in the male rats (generally regarded as more sensitive than female rats to experimental tubular neoplasias) used in this study; 5. the negative genetic toxicology database; 6. the previously reported chronic studies which were all negative for carcinogenicity; and 8. the judgement that the dose chosen was a good approximation of the maximum tolerated dose (MTD).

Based on these considerations and conclusions of the *ad hoc* NTP Peer Review Panel of Experts, the FDA concluded that FD&C Yellow No. 6 when fed in the diet of laboratory animals does not induce carcinogenic activity in the kidneys or any other site. The ANS Panel agreed with this conclusion.

Furthermore, the ANS Panel agreed with the conclusion in the FDA Final Rule on the permanent listing of FD&C Yellow No. 6 for use generally in food drugs and cosmetics, that based on the occurrence of the adverse effect on pup body weight gain observed in rats during the last part of lactation in the group fed 1.5 % FD&C Yellow No. 6 in the diet, the NOAEL of this study is 0.75 % (equivalent to 375 mg/kg bw/day).

2.2.2. Additional toxicological data published after the 2009 ANS Panel opinion

An extensive literature search was performed on three electronic databases (PubMed, Web of Science, Toxnet) covering the time period between approximately one year before the adoption of the opinion (i.e. 1 November 2008 until 31 December 2013), aiming to retrieve any relevant toxicological data that should be taken into account in the current opinion. Details of the search strings used are shown in Appendix 1.

The safety of Sunset Yellow FCF, with particular respect to the data on its metabolism, genotoxicity and carcinogenicity, had already been reviewed by the ANS Panel in the context of the recent assessment of Allura Red AC and other structurally related sulphonated mono azo dyes (EFSA ANS Panel, 2013). The following additional publications were retrieved in the updated literature search.

2.2.2.1. *In vivo* studies

No new studies on ADME, repeat-dose toxicity or reproductive and developmental toxicity were identified following the aforementioned updated literature search.

Genotoxicity

An updated literature search covering genotoxicity studies had already been conducted in the context of the recent assessment of Allura Red AC and other structurally related sulphonated mono azo dyes (EFSA ANS Panel, 2013). The additional extensive literature search did not reveal any new data in addition to those already considered in the statement on Allura Red AC and other structurally related sulphonated mono azo dyes (EFSA ANS Panel, 2013).

Immunotoxicity

A study was carried out to investigate the effect of oral administration of Amaranth, Sunset Yellow and Curcumin on immunological responses (Hashem et al., 2010). The food colours were administered daily by gavage to female Sprague Dawley albino rats (n=10) for 4 weeks: Sunset Yellow FCF was administered at a dose of 315 mg/kg bw/day. After the two weeks of treatment all the animals were immunostimulated by i.p. injection of 10 % sheep RBC suspension (1 ml/rat). A group of non-sensitized rats was used as the control. Body weight, relative body weight, total and differential leukocytes count, mononuclear cell count, delayed hypersensitivity, total protein and serum fractions, were determined. Results revealed that oral administration of Sunset Yellow did not affect the body weight gain or the spleen weight. On the other hand, Sunset Yellow significantly decreased the weight of thymus gland of the rats. Total leukocyte count was not affected. Moreover, oral administration of Sunset Yellow revealed a significant decrease in circulating mononuclear cells in peripheral blood. Sunset Yellow significantly decreased the delayed hypersensitivity. Total serum protein, albumin, total globulin and albumin/globulin (A/G) ratio were not affected by administration of the colouring agent. The authors concluded that Sunset Yellow used at dose of 315 mg/kg bw/day exerted a depressing effect on the cellular, but not humoral, immune response. The Panel noted that this study was conducted with locally sourced uncharacterised material of unknown purity and therefore was not considered suitable for risk assessment.

Neurodevelopmental toxicity and neurobehavioural studies

Some studies by the same research group aimed at investigating neurodevelopmental toxicity and conducted with mixtures of food additives, locally sourced and of unknown purity, were retrieved (Ceyhan et al., 2013; Doguc et al., 2013a, 2013b).

In the study by Ceyhan et al. (2013), a mixture of authorised food colours (Sunset Yellow FCF, 2.5 mg/kg bw, Allura Red, 7 mg/kg bw/day, Erythrosin, 0.1 mg/kg bw/day, Ponceau 4R, 4 mg/kg bw/day, Tartrazine, 7.5 mg/kg bw/day, Amaranth, 0.5 mg/kg bw/day, Brilliant Blue 12.5 mg/kg bw/day, Azorubine, 4 mg/kg bw/day and Indigotine 5 mg/kg bw/day, purity of the test material not known) was administered to female rats one week before mating, during mating and during the gestation period at doses corresponding to the respective ADIs. The effects of intrauterine exposure of synthetic food colours on expression of N-methyl-D-aspartate receptors (NMDARs) subunits (NR2A and NR2B) and nicotinic acetylcholine receptors (nAChRs) subunits α7, α4, ß2 were investigated in their offspring when they became adults. The results indicated that exposure to the mixture of food colours during the fetal period may lead to alterations in expressions of NMDARs and nAChRs in adulthood, and the alterations were totally different between males and females. Exposure to the mixture of food colours in male rats led to an increase in expression of NR2B and AChR b2 receptor subunits and a decrease in nAChR a4 subunits. On the other hand, the main effect of food colours administered to female rats was a significant reduction in NR2B expression.

Two other publications by the same research group (Doguc et al., 2013a, 2013b) investigated the effects of the same mixture of authorised food colours (Sunset Yellow FCF, Allura Red, Erythrosine, Ponceau 4R, Tartrazine, Amaranth, Brilliant Blue, Azorubine and Indigotine, purity of the test material not known) administered to female rats before and during gestation at doses corresponding to the respective ADIs (in the case of Sunset Yellow FCF 2.5 mg/kg bw/day) on spatial working memory and behaviour in their offspring, as measured by Morris water maze and by open-field test and forced swim test, respectively. No adverse effects on spatial working memory and on behaviour were observed in offspring, but some parameters of locomotor activity were found to be increased.

The Panel noted that these studies were conducted with locally sourced uncharacterised material of unknown purity and therefore were not considered suitable for risk assessment.

2.2.2.2. *In vitro* studies

Neurotoxicity

In the study by Park et al. (2009), the effects of the food colours Sunset Yellow FCF (obtained from Sigma Chemical Co. (St. Louis, MO)), Allura Red, Tartrazine, Amaranth and Brilliant Blue alone and in combination were tested on both multipotent, immortalized C17.2 cells as a model for developmental effects, and adult neural stem cells in the hippocampus as a model for adult hippocampal neurogenesis. No significant effects were observed for Sunset Yellow FCF.

Immunotoxicity

The immunotoxic properties of Sunset Yellow FCF have been investigated in isolated mice splenocytes (Yadav et al., 2013). Sunset Yellow (purity not stated, from Sarabhai Chemicals, Mumbai) did not exhibit cytotoxicity up to 250 µg/ml after 72 hours of treatment (cytotoxicity measured as PI staining and MTT assay). This dose was therefore chosen for further studies on functional responses of T-cells and B-cells. The results showed that Sunset Yellow FCF at the non-cytotoxic dose of 250 µg/ml significantly suppressed the mitogen-induced proliferation of splenocytes and MLR response. Further immunophenotypic analysis revealed that Sunset Yellow FCF alters the relative expression of CD3e/CD4/CD8 in T cells and CD19 in B-cells. Consistent with the suppression of T-cell and B-cell responses and altered surface receptor expression, Sunset Yellow FCF also lowered the expression of IL2, IL4, IL6, IL-17, IFN- and TNF- cytokines.

Oestrogenic activity

A reporter gene assay in the human breast cancer cell line MCF-7 transiently transfected with luciferase reporter gene construct under control of a concatemer of 3 oestrogen response elements and a thymidine kinase promoter was used by Axon et al. (2012) to screen for chemical compounds which have the potential to modulate human oestrogen receptor (ER) transcriptional activity. Amongst the chemicals tested in this assay was the food colour Sunset Yellow FCF, which showed xenoestrogenic activity with EC50 % at concentration of 220 nM. In addition, Sunset Yellow FCF treatment significantly induced the expression of trefoil factor 1 (TFF1) mRNA as determined by quantitative RT-PCR. TFF1 has been previously shown to be an ER-inducible gene in MCF-7 cells (May and Westley, 1988)

The Panel noted however, that the test method used in the study, although widely used in the scientific community, is not an OECD validated method, in contrast to the BG1Luc oestrogen receptor transcriptional activation (TA) test method for identifying ER agonists and antagonists (OECD TG 457 or OECD TG 455).

2.2.2.3. Human data

A case-report of allergic contact dermatitis was reported in one patient after application on the skin of an antiseptic solution containing Sunset Yellow FCF (Mc Cleskey, 2011). The Panel noted that the route of exposure in this single case-report was not relevant for the assessment of Sunset Yellow FCF as a food additive and that the relevance of dermal sensitization reactions for oral sensitization has not been established.

3. Exposure assessment of Sunset Yellow (E 110)

3.1. Previous exposure assessment of Sunset Yellow FCF (E 110)

In its 2009 opinion, the ANS Panel had evaluated the exposure to Sunset Yellow FCF (E 110) on the basis of the uses and use levels authorised in the legislation[7] and the reported use levels, as identified by the Panel from the data made available by industry and other relevant stakeholders.

Refined exposure estimates had been performed both for children and the adult population according to the Tier 2 and Tier 3 approaches described in the SCOOP Task 4.2, which combines, respectively, detailed individual food consumption information from the population with the Maximum Permitted Levels (MPLs) of use, as specified in the Directive 94/36/EC on food colours (Tier 2), and with the maximum reported use levels of Sunset Yellow FCF, as identified by the Panel from the data made available (Tier 3). Data for some of the authorised uses of Sunset Yellow FCF had been provided by the Confederation of the Food and Drink Industries of the EU (CIAA, now FoodDrinkEurope), the Union of European Beverages Associations (UNESDA), the European Spirits Organisation (CEPS) and the Federation of European Food Additives, Food Enzymes and Food Culture Industries (ELC). Additional data had been made available by the UK Food Standards Agency (FSA), the Food Safety Authority of Ireland (FSAI) and the Agence Française de Sécurité Sanitaire des Aliments (AFSSA, now ANSES).

The Panel concluded that at the maximum reported levels of use of Sunset Yellow FCF, refined intake estimates were generally below the temporary ADI of 1 mg/kg bw/day, although in 1- to10-year old children the mean and the high percentiles of exposure (95^{th}/97.5^{th}) could be higher than this ADI, at the upper end of the range (Table 1). The main contributors to the total anticipated exposure (>10 % in all countries) were soft drinks, desserts, including flavoured milk products, sauces, seasonings (e.g. curry powder, tandoori), pickles, relishes, chutney, piccalilli and fine bakery wares.

Table 1: Summary of anticipated exposure to Sunset Yellow FCF (E 110) in children and the adult population (mg/kg bw/day) (EFSA ANS Panel, 2009)

	Adult UK population[(a)] (> 18 years old)	**Pre-school UK children[(a)]** (1.5-4.5 years old, 15 kg body weight)	**Children EXPOCHI population[(b)]** (1-10 years old, 25-30 kg body weight)
Maximum permitted levels			
• Mean exposure	0.5	1.4	0.3 – 2.5
• Exposure 95^{th} or 97.5^{th} percentile[(a)]	1.1	3.5	0.7 – 6.7
Maximum reported use levels			
• Mean exposure	0.3	1.1	0.2 – 2.1
• Exposure 95^{th} or 97.5^{th} percentile[(a)]	0.9	3.2	0.6 – 5.8

(a): For UK, estimates are based on the UNESDA report which gives the 97.5^{th} percentile intake from beverages plus *per capita* average from the rest of diet (Tennant, 2006).
(b): For EU children, estimates are based on the EXPOCHI report, which gives the 95^{th} percentile intake.

In 2011, EFSA carried out a revised exposure assessment of Sunset Yellow FCF (E 110) from its use as a food additive, in children, based on the revised proposed use levels as requested by the European Commission (EFSA, 2011a). The revised use levels proposed were lower for all food categories compared to those considered in the former EFSA evaluation (EFSA ANS Panel, 2009), and 18 food uses previously permitted, were withdrawn Four different scenarios had been considered, differing only in the MPLs proposed for the use of Sunset Yellow FCF in flavoured drinks: 10, 15, 18 and 20 mg/l respectively. Revised exposure estimates have been calculated for Tier 2 applying the same

[7] European Parliament and Council Directive 94/36/EC of 30 June 1994 on colours for use in foodstuffs. OJ L 237, 10.9.1994, p. 13.

methodology used by the ANS Panel for the re-evaluation of food colours, based on the proposed revised use levels, combined with food consumption data for children.

The mean anticipated dietary exposure to Sunset Yellow FCF in European children (aged 1-14 years) ranged from 0.02 to 0.4 mg/kg bw/day, and the high level estimates ranged from 0.08 to 1.2 mg/kg bw/day. The main contributors (>10 % in all countries) to the total anticipated exposure to Sunset Yellow FCF of European children were non-alcoholic flavoured drinks and desserts, including flavoured milk products. It was concluded that, for all scenarios, the high level exposure estimates for children calculated on the basis of the proposed revised MPLs, were below the temporary ADI of 1 mg/kg bw/day for all European countries considered (maximum of 0.8 mg/kg bw/day), except for UK pre-school children, who might slightly exceed the ADI in scenarios 3 and 4 (1.1 and 1.2 mg/kg bw/day, respectively).

3.2. Maximum Permitted Levels of use of Sunset Yellow FCF (E 110)

Maximum Permitted Levels (MPLs) of use for Sunset Yellow (E 110) have been defined in Annex II of Regulation (EC) No 1333/2008[8] of the European Parliament and of the Council Commission on food additives.

Currently Sunset Yellow FCF (E 110) is a food colour authorised in the EU with MPLs ranging from 5 to 200 mg/kg in foods (Table 2).

Table 2 summarises foods that are permitted to contain Sunset Yellow and the corresponding MPLs as set by Annex II of Regulation (EC) No 1333/2008.

Table 2: MPLs of Sunset Yellow (E 110) in foods according to the Annex II of Regulation (EC) No 1333/2008

FCS Category No	Food categories	Restrictions/exception	Current MPL (mg/l or mg/kg as appropriate)	Previous MPL (mg/l or mg/kg as appropriate)
1.4	**Flavoured fermented milk products including heat treated products**		5 (a)	150
1.6.3	**Other creams**	only flavoured creams	5 (a)	150
4.2.4.1	**Fruit and vegetable preparations excluding compote**	only *mostarda di frutta*	35 (a)	200
5.2	**Other confectionery including breath freshening microsweets**	except candied fruit and vegetables; traditional sugar coated nut- or cocoa-based confectionery of almond shape or host shape, typically longer than 2 cm and typically consumed at celebratory occasions, i.e. weddings, communion, etc.	35 (a)	300
5.2	**Other confectionery including breath freshening microsweets**	only candied fruit and vegetables	10 (a)	200
5.2	**Other confectionery including breath freshening microsweets**	only traditional sugar coated nut- or cocoa-based confectionery of almond shape or host shape, typically longer than 2 cm and typically consumed at	50 (a)	N/A

[8] Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives. OJ L 354, 31.12.2008, p. 16.

FCS Category No	Food categories	Restrictions/exception	Current MPL (mg/l or mg/kg as appropriate)	Previous MPL (mg/l or mg/kg as appropriate)
		celebratory occasions, i.e. weddings, communion, etc.		
5.3	**Chewing gum**		10 [a]	300
5.4	**Decorations, coatings and fillings, except fruit based fillings covered by category 4.2.4**	only decorations, coatings and sauces, except fillings	35 [a]	500
5.4	**Decorations, coatings and fillings, except fruit based fillings covered by category 4.2.4**	only fillings	35 [a]	300
6.6	**Batters**		35 [a]	500
8.2.1	**Non-heat-treated processed meat**	only *sobrasada*	15	135
8.2.3	**Casings and coatings and decorations for meat**	only decorations and coatings except edible external coating of *pasturmas*	35 [a]	500
9.2.	**Processed fish and fishery products including molluscs and crustaceans**	only in salmon substitutes based on *Theragra chalcogramma* and *Pollachius virens*	200 [b]	N/A
9.3	**Fish roe**	except Sturgeons' eggs (Caviar)	200 [a]	300
12.4	**Mustard**		50 [a]	300
12.6	**Sauces**	only in pickles and piccalilli	30 [c]	N/A
12.9	**Protein products, excluding products covered in category 1.8**	only meat and fish analogues based on vegetable proteins	20 [a]	100
13.2	**Dietary foods for special medical purposes defined in Directive 1999/21/EC (excluding products from food category 13.1.5)**		10 [a]	50
13.3	**Dietary foods for weight control diets intended to replace total daily food intake or an individual meal (the whole or part of the total daily diet)**		10 [a]	50
14.1.4	**Flavoured drinks**	excluding chocolate milk and malt products	20 [a]	100
14.2.3	**Cider and perry**	excluding *cidre bouché*	10 [c]	200
14.2.4	**Fruit wine and made wine**		10 [a]	200
14.2.6	**Spirit drinks as defined in Regulation (EC) No 110/2008**	except: spirit drinks as defined in Article 5(1) and sales denominations listed in Annex II, paragraphs 1-14 of Regulation (EC) No 110/2008 and spirits (preceded by the name of the fruit) obtained by maceration and distillation, Geist (with the name of the fruit or the raw material used), London Gin, Sambuca, Maraschino, Marrasquino or Maraskino and Mistrà	100 [a]	200
14.2.7.1	**Aromatised wines**	except *americano, bitter vino*	50 [a]	200
14.2.7.1	**Aromatised wines**	only *bitter vino*	50 [d]	100
14.2.7.2	**Aromatised wine-based drinks**	except *bitter soda, sangria, claria, zurra*	50 [a]	200
14.2.7.2	**Aromatised wine-based drinks**	only *bitter soda*	50 [e]	100

FCS Category No	Food categories	Restrictions/exception	Current MPL (mg/l or mg/kg as appropriate)	Previous MPL (mg/l or mg/kg as appropriate)
14.2.7.3	**Aromatised wine-product cocktails**		50 (a)	200
14.2.8	**Other alcoholic drinks including mixtures of alcoholic drinks with non-alcoholic drinks and spirits with less than 15% of alcohol**	only alcoholic drinks with less than 15 % of alcohol	100 (a)	200
16	**Desserts excluding products covered in category 1, 3 and 4**		5 (a)	150
17.1	**Food supplements supplied in a solid form including capsules and tablets and similar forms excluding chewable forms**		10 (a)	300
17.2	**Food supplements supplied in a liquid form**		10 (a)	100
17.3	**Food supplements supplied in a syrup-type or chewable form**	only liquid food supplements	10 (a)	300

N/A: not applicable

(a): The total quantity of E 104, E 110, E 124 and the colours in Group III shall not exceed the maximum listed for Group III.
(b): The total quantity of E 110, E 124 and the colours in Group III shall not exceed the maximum listed for Group III.
(c): The total quantity of E 104 and E 110 and the colours in Group III shall not exceed the maximum listed for Group III.
(d): In bitter vino E 100, E 101, E 102, E 104, E 110, E 120, E 122, E 123, E 124, E 129 are authorised individually or in combination.
(e): In bitter soda E 100, E 101, E 102, E 104, E 110, E 120, E 122, E 123, E 124, E 129 are authorised individually or in combination.

Sunset Yellow (E 110) may also be used in the form of aluminium lakes (Regulation (EC) No 1333/2008).

3.3. Reported use levels or data on analytical levels of sunset yellow

Most food additives in the EU are authorised at a specific MPL. However, a food additive may be used at a lower level than the MPL. For those additives where no MPL is set and which are authorised as *quantum satis* (QS), information on actual use levels is required for performing an exposure assessment.

In the framework of Regulation (EC) No 1333/2008 on food additives and of Commission Regulation (EU) No 257/2010[9] regarding the re-evaluation of approved food additives, EFSA issued a public call[10] for food additives usage level and/or concentration data in March 2013, with deadline at the end of November 2013. Data on Sunset Yellow FCF (E 110) including present use and use patterns (i.e. which food categories and subcategories, proportion of food within categories/subcategories in which it is used, actual use levels (typical and maximum use levels) were requested from relevant stakeholders. European food manufacturers, national food authorities, research institutions, academia, food business operators and any other interested stakeholders were invited to submit analytical data on Sunset Yellow FCF in foods. The data submission to EFSA followed the requirements of the EFSA Guidance on Standard Sample Description for Food and Feed (EFSA, 2010).

[9] Commission Regulation (EU) No 257/2010 of 25 March 2010 setting up a programme for the re-evaluation of approved food additives in accordance with Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives. OJ L 80, 26.03.2010, p. 19.

[10] Call for food additives usage level and/or concentration data in food and beverages intended for human consumption. Published: 27 March 2013. http://www.efsa.europa.eu/en/data/call/130327.htm

It should be noted that in 2012, following the conclusions of the EFSA Opinion on Sunset Yellow adopted in 2009 by the ANS Panel, the Annex II of Regulation (EC) No 1333/2008 was amended as regards the conditions of use and the use levels for Sunset Yellow FCF (E 110), Quinoline Yellow (E 104) and Ponceau 4R (E 124) (Commission Regulation (EU) No 232/2012[11]). For Sunset Yellow FCF, MPLs, when not withdrawn (n=18), were decreased by a factor of 2 to 30, depending on the food category, applicable from 1 June 2013 (Table 2).

Appendix B provides data on the use levels of Sunset Yellow FCF in foods as reported by industry and on analysed levels as provided by Member States. The Panel noted that usage or analytical values which were collected before June 2013 may not be up-to-date with regards to the amendments made in the legislation (i.e. in some cases result above the MPLs currently authorised for Sunset Yellow FCF).

Summarised data on reported use levels of Sunset Yellow FCF in foods provided by industry

Data on six out of the 41 food categories in which Sunset Yellow (E 110) is currently authorised as a food additive were provided to EFSA by the industry.

Updated information on the actual use levels of Sunset Yellow FCF in foods was made available by FoodDrinkEurope (FDE) for the following food categories of finished products: batters (FCS Category 6.6), *Sobrasada* (FCS Category 8.2.1), Casings and coatings and decorations for meat (FCS Category 8.2.3), Sauces (FCS Category 12.6), and flavoured drinks (FCS Category 14.1.4). Additional information on the usage levels of Sunset Yellow FCF in chewing gum (FCS Category 5.3) was provided by the International Chewing Gum Association (ICGA).

Summarised data on concentration levels of Sunset Yellow FCF in foods provided by MS

Additionally, analytical results from Member States were collected through the call launched by EFSA in March 2013. In total, 6522 analytical values were reported to EFSA. The foods analysed were sampled in Germany (n=3839), Austria (n=998), Slovakia (n=675), Hungary (n=371), Czech Republic (n=328), Ireland (n=206), Cyprus (n=77) and Spain (n=28) between the years 2001 to 2013.

Data were mainly provided on flavoured drinks (FCS Category 14.1.4), other confectionery including freshening micro-sweets (excluding candied fruit and vegetables and dragées) (FCS Category 5.2), and alcoholic drinks (FCS Categories 14.2.4, 14.2.6, 14.2.7.2, 14.2.7.3 and 14.2.8). Analytical values in food categories in which Sunset Yellow FCF is not authorised (n=3148) were also provided.

Out of the remaining samples (n=3374), 1712 were below the LOD, 388 below the LOQ, 531 were quantitative values (indication of absence or presence of Sunset Yellow FCF in the food) and 743 are numerical values. Only 42 analytical results received from the Member States regarded food items sampled in 2013 and only 11 were sampled after 1 June 2013. In the absence of more recent data, data collected before 2013 were also considered for the refined exposure assessment scenario, provided that the values were below the currently authorised MPLs of use of Sunset Yellow FCF.

3.4. Refined exposure assessment of Sunset Yellow FCF (E 110)

3.4.1. Food consumption data used for exposure assessment

Since 2010, the EFSA Comprehensive European Food Consumption Database (Comprehensive Database) has been populated with data from national information on food consumption at a detailed level. Competent authorities in the European countries provide EFSA with data on the level of food consumption by the individual consumer from the most recent national dietary survey in their country

[11] Commission Regulation (EU) No 232/2012 of 16 March 2012 amending Annex II to Regulation (EC) No 1333/2008 of the European Parliament and of the Council as regards the conditions of use and the use levels for Quinoline Yellow (E 104), Sunset Yellow FCF/Orange Yellow S (E 110) and Ponceau 4R, Cochineal Red A (E 124). OJ L 78, 17.3.2012, p.1.

(cf. Guidance of EFSA 'Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment' (EFSA, 2011b)).

The food consumption data gathered by EFSA were collected using different methodologies and thus direct country-to-country comparison should be made with caution.

For calculation of chronic exposure, intake statistics have been calculated based on individual average consumption over the total survey period excluding surveys with only one day per subject, considered as not adequate to assess repeated dietary exposure, as suggested by the EFSA Working Group on Food Consumption and Exposure (EFSA, 2011b). High level consumption was only calculated for those foods and population groups where the sample size was sufficiently large to allow calculation of the 95th percentile (EFSA, 2011b). The Panel estimated chronic exposure for the following population groups: toddlers, children, adolescents, adults and the elderly. Calculations were performed using individual body weights.

Thus, for the present assessment, food consumption data were available from 26 different dietary surveys carried out in 17 European countries as mentioned in Table 3:

Table 3: Population groups considered for the exposure estimates of sunset yellow (E 110)

Population	Age range	Countries with food consumption surveys covering more than one day
Toddlers	from 12 up to and including 35 months of age	Belgium, Bulgaria, Finland, Germany, Italy, the Netherlands, Spain
Children[12]	from 36 months up to and including 9 years of age	Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Latvia, Netherlands, Spain, Sweden
Adolescents	from 10 up to and including 17 years of age	Belgium, Cyprus, Czech Republic, Denmark, France, Germany, Italy, Latvia, Spain, Sweden
Adults	from 18 up to and including 64 years of age	Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Netherlands, Spain, Sweden, UK
The elderly[12]	from 65 years of age and older	Belgium, Denmark, Finland, France, Germany, Hungary, Italy

Consumption records were codified according to the FoodEx classification system (EFSA, 2011c). Nomenclature from the FoodEx classification system has been linked to the Food Categorisation System (FCS) as presented in the Annex II of Regulation (EC) No 1333/2008, part D, to perform exposure estimates. In practice, FoodEx food codes were matched to the FCS food categories and the exposure was calculated by multiplying MPLs and values reported in Appendix B for each food group with their respective consumption amount per kg body weight (bw) separately for each individual in the database, calculating the sum of exposure for each survey day for the individual, and then deriving the daily mean for the survey period. Based on the individual exposures, the mean and 95th percentile exposure was calculated for the total survey population separately for each survey and for the five population groups described in Table 3.

High percentile exposure was only calculated for those foods and population groups were the sample size was sufficiently large to allow calculation of the 95th percentile of exposure (EFSA, 2011c). Therefore, in the present assessment, high levels of exposure for toddlers from Belgium, Italy and Spain were not included.

[12] The terms "children" and "the elderly" correspond respectively to "other children" and the merge of "elderly" and "very elderly" in the Guidance of EFSA on the 'Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment' (EFSA, 2011b).

3.4.2. Food items selected for the refined exposure assessment of Sunset Yellow FCF (E 110)

The food categories in which the use of Sunset Yellow FCF (E 110) is authorised were selected from the nomenclature of the EFSA Comprehensive Database (FoodEx classification system food codes), at a detailed level (up to FoodEx Level 4) (EFSA, 2011c).

Some food items are not referenced in the EFSA Comprehensive Database and therefore could not be taken into account in the present estimate, as described below. This results in an underestimation of the exposure.

- 4.2.4.1. Fruit and vegetable preparations excluding compote, only *mostarda di frutta*
- 5.4. Decorations, coatings and fillings, except fruit based fillings covered by category 4.2.4, only decorations, coatings and sauces, except fillings, and only fillings
- 6.6. Batters
- 8.2.3. Casings and coatings and decorations for meat, only decorations and coatings except edible external coating of *pasturmas.*

For the food category 1.6.3 Other creams, only flavoured creams: the sub-group other cream is not distinguishable from other kinds of cream; the same applies in differentiating flavoured cream from plain cream. In order to avoid a large overestimation by taking into account the whole food group of cream and cream powder (FCS 1.6), the flavoured creams were not taken into account in the present estimate.

For some other food categories, the restrictions which apply to the use of Sunset Yellow FCF could not be taken into account, and therefore the whole food category with the highest use level (MPL or reported) was considered for the exposure estimates as described below. This results in an overestimation of the exposure:

- 9.3. Fish roe, except Sturgeons' eggs (Caviar): this exception could not be taken into account in the present exposure assessment, since no distinction is made in the FoodEx nomenclature between sturgeons' eggs and other fish eggs.
- 14.2.3. Cider and perry: no distinction was possible between cider and *cidre bouché*.
- 14.2.7.1. Aromatised wines and 14.2.7.2. Aromatised wine-based drinks: no distinction is possible between *americano* and other products and *bitter soda* and other products of each food category.

3.5. Dietary exposure assessment

3.5.1. Exposure to Sunset Yellow FCF (E 110) from its use as food additive

Exposure to Sunset Yellow FCF (E 110) from its use as a food additive was calculated using MPLs as listed in Table 2 and using reported use level as listed in Appendix B. The Panel noted that these exposure estimates should be considered conservative, as it is assumed that all processed foods can contain Sunset Yellow at the MPLs or at the maximum reported use levels in all food categories in which it is authorised.

Table 4 summarises the estimated exposure to Sunset Yellow from its use as a food additive of all five population groups. Detailed results by age class and survey are presented in Appendix C.

Table 4: Summary of anticipated exposure to Sunset Yellow FCF (E 110) from its use as a food additive using MPLs and reported use levels in five population groups (min-max across the dietary surveys in mg/kg bw/day)

	Toddlers (12-35 months)	Children (3-9 years)	Adolescents (10-17 years)	Adults (18-64 years)	The elderly (>65 years)
Estimated exposure using MPLs					
• Mean	0.02-0.4	0.03-0.3	0.03-0.2	0.01-0.1	<0.01-0.03
• High level[13]	0.1-0.6	0.1-0.8	0.1-0.5	0.1-0.4	0.02-0.1
Estimated exposure using reported use levels					
• **Mean**	0.01-0.3	0.02-0.3	0.03-0.2	0.01-0.1	<0.01-0.02
• **High level**[13]	0.02-0.6	0.1-0.7	0.1-0.4	0.1-0.4	0.02-0.1

3.5.2. Main food categories contributing to exposure to Sunset Yellow FCF (E 110)

Table 5: Main food categories contributing to exposure to Sunset Yellow FCF using MPLs (> 5 % to the total mean exposure) and number of surveys in which each food category is contributing

FCS Category Number	Foods	Toddlers	Children	Adolescents	Adults	The elderly
		range of % contribution to the total exposure (Number of Surveys)[(a)]				
1.4	**Flavoured fermented milk products including heat-treated products**	8.7 – 74.0 (6)	5.3 – 20.2 (12)	5.2 -8.5 (3)	7.2– 12.2 (3)	6.7 – 18.6 (4)
5.2	**Other confectionery including breath freshening microsweets**	5.1-8.1 (5)	6.0-17.7 (9)	7.5-8.2 (4)	5.8 – 11.3 (3)	5.1 – 7.0 (3)
9.3	**Fish roe**		5.6 (1)		6.5 (1)	5.6 (1)
12.4	**Mustard**					5.1 (1)
12.9	**Protein products, excluding products covered in category 1.8**					6.2 (1)
14.1.4	**Flavoured drinks**	24.4 – 88.9 (6)	60.5 – 95.0 (15)	81.3 – 94.4 (12)	47.3 – 91.0 (15)	20.7 – 88.8 (7)
14.2	**Alcoholic beverages**			9.0 (1)	5.6 – 41.0 (12)	15.1 – 53.2 (6)
16	**Desserts excluding products covered in category 1, 3 and 4**	7.0 – 20.8 (2)	5.0 -7.4 (2)			6.7 (1)

(a): The total number of surveys may be greater than the total number of countries as listed in Table 3, as some countries submitted more than one survey for a specific age range.

[13] typically 95th percentile of consumers only

3.5.3. Main food categories contributing to exposure of Sunset Yellow FCF (E 110) using reported use levels or analytical levels

Table 6: Main food categories contributing to exposure to Sunset Yellow FCF using reported use levels or reported data on analytical levels (> 5 % to the total mean exposure) and number of surveys in which each food category is contributing

FCS Category Number	Foods	Toddlers	Children	Adolescents	Adults	The elderly
		range of % contribution to the total exposure (Number of Surveys)[a]				
5.2	**Other confectionery including breath freshening microsweets**	7.7-22.3 (6)	6.6-22.5 (9)	5.0-8.5 (6)	5.0 – 17.0 (4)	7.0 – 13.6 (3)
9.3	**Fish roe**					5.0 (1)
14.1.4	**Flavoured drinks**	81.4 – 97.7 (6)	76.7 – 96.5 (15)	89.1 – 98.6 (12)	71.0 – 98.2 (15)	42.3 – 97.2 (7)
14.2	**Alcoholic beverages**				5.1 – 22.7 (8)	5.9 – 40.8 (6)
16	**Desserts excluding products covered in category 1, 3 and 4**	7.6 – 77.7 (2)	5.3 -7.0 (2)			11.8 (1)

(a): The total number of surveys may be greater than the total number of countries as listed in Table 3, as some countries submitted more than one survey for a specific age range.

3.6. Uncertainty analysis

Uncertainties in the exposure assessment of Sunset Yellow FCF (E 110) have been discussed above. According to the guidance provided in the EFSA opinion related to uncertainties in dietary exposure assessment (EFSA, 2007), the following sources of uncertainties have been considered and summarised below:

Table 7: Qualitative evaluation of influence of uncertainties

Sources of uncertainties	Direction[a]
Consumption data: different methodologies / representativeness / under reporting / misreporting / no portion size standard	+/-
Use of data from food consumption survey of few days to estimate long-term (chronic) exposure	+
Correspondence of reported use levels to the food items in the EFSA Consumption Database: uncertainties on which precise types of food the use levels refer.	+/-
Use of the FAIM tool nomenclature (FoodEx level 2) for some food categories	+
Occurrence data: maximum reported use levels considered applicable for all items within entire food category, exposure calculations based on the maximum levels (permitted and reported use from industries or analytical from MS)	+
Uncertainty in possible national differences in use levels of food categories, concentration data not fully representative of foods on the EU market	+/-

(a): + = uncertainty with potential to cause over-estimation of exposure; - = uncertainty with potential to cause underestimation of exposure.

4. Discussion

In 2009, the ANS Panel requested a 28-day study with Sunset Yellow FCF to be performed, in accordance with OECD guidelines, and with well-defined material, in order to clarify the histopathological changes in the testes and the changes in the blood lipid profile observed by Mathur el al. (2005a, 2005b) in rats, after 90-day dietary exposure to dose levels equivalent to 250 and 1500 mg Sunset Yellow FCF/kg bw/day. Furthermore, the test material in the Mathur studies was not characterised and was bought on the local market. A 28-day study was considered sufficient to study the effects on the testis, as no effects on fertility in a reproductive toxicity study in rats, and no relevant histopathological changes were reported in long-term studies in mice and rats (EFSA ANS Panel, 2009). The Panel noted that a 28-day study would also be sufficient for considering the effects reported on the blood lipid profile.

The results reported by Mathur et al. (2005a, 2005b) on lipid profile and testes histopathology were not confirmed in a dietary 28-day study in male Hsd:SD® rats performed by Product Safety Labs (2012) according the current OECD guidelines and with levels of up to 18 000 mg Sunset Yellow FCF/kg diet (equivalent to 1 475 mg/kg bw/day). The Panel agreed with the authors of the 28-day study that the NOAEL of this study was 18 000 mg/kg diet (equivalent to 1 475 mg/kg bw/day), the highest dose level tested. The Panel noted that the material tested in this 28-day study met the EU specifications for Sunset Yellow FCF as a food additive. The Panel, based on the data described in its 2009 opinion and the results from this new 28-day study, concluded that the findings of the Mathur studies (2005a, 2005b) should be disregarded for the risk assessment of Sunset Yellow FCF.

The ANS Panel noted that in 2011 JECFA withdrew the previously set ADI for Sunset Yellow FCF, and established a new ADI of 0-4 mg/kg bw/day (JECFA, 2011). This latest evaluation performed by JECFA encompassed previously reviewed data, published information that had become available since Sunset Yellow FCF was last considered by the Committee, and a comprehensive review of one unpublished long-term feeding study in mice and two studies in rats provided by the United States Food and Drug Administration (FDA).

The Panel evaluated the above mentioned long-term feeding studies and concluded that no carcinogenic potential of Sunset Yellow FCF/ FD&C Yellow No. 6 was observed in mice and rats. Based on the occurrence of the adverse effect on pup body weight gain, observed during the last part of the lactation in a long-term rat study in the group fed 1.5 % FD&C Yellow No. 6 in the diet, and described in the full reports provided by the FDA, the Panel agreed with JECFA that the NOAEL for this study is 0.75% (equivalent to 375 mg/kg bw/day). The Panel considered that, this NOAEL being obtained from a long-term study including an *in utero* phase, an uncertainty factor of 100 can be applied for the derivation of a new ADI of 4 mg/kg bw/day. The Panel noted that in its latest evaluation of Sunset Yellow FCF, JECFA reached similar conclusions (JECFA, 2011).

The following additional studies were detected in an extensive literature search which was performed on three electronic databases (PubMed, Web of Science, Toxnet) covering the time span between approximately one year before the adoption of the opinion of the ANS Panel (EFSA ANS Panel, 2009) (i.e. from 1 November 2008 until 31 December 2013), aiming to retrieve any relevant toxicological data that should be taken into account for the current opinion.

No new data on genotoxicity were retrieved, in addition to those already considered in the statement on Allura Red AC and other structurally related sulphonated mono azo dyes (EFSA ANS Panel, 2013).

A study was carried out to investigate the effect of oral administration of Amaranth, Sunset Yellow FCF and Curcumin on immunological responses (Hashem et al., 2010). Sunset Yellow (315 mg/kg bw/day) was administered by gavage to female Sprague Dawley albino rats for 4 weeks. The authors stated that Sunset Yellow used at a dose of 315 mg/kg bw/day exerted a depressing effect on the cellular, but not humoral, immune response. The Panel noted that this study was conducted with

locally sourced uncharacterised material of unknown purity and did not consider this study suitable for risk assessment.

Oestrogenic activity of Sunset Yellow FCF was demonstrated in an *in vitro* model system (Axon et al., 2012). According to EFSA's Scientific Opinion on the hazard assessment of endocrine disruptors (EFSA SC, 2013) *"the fact that a substance in an in vitro assay is binding to an endocrine receptor, then interfering with the intracellular messenger system connecting receptor to target, or resulting in an endocrine-related response in a target cell, must be taken as strong indication for endocrine activity. If a suitable animal model provides further indication for an endocrine-related adverse effect, this substance should be considered an endocrine disruptor"*. However, in long-term studies including an *in utero* phase in mice and rats, no effects on endocrine and reproductive organs were observed. Therefore, the results of this *in vitro study* were not further considered in the risk assessment.

A refined exposure assessment for Sunset Yellow FCF (E 110) has been performed taking into consideration the MPLs of use currently authorised in Annex II of Regulation (EC) No 1333/2008. Overall, exposure estimates for Sunset Yellow FCF (E 110) based on the currently authorised MPLs of use in foods are well below the new ADI of 4 mg/kg bw/day, established by the ANS Panel, for all population groups.

The results of the present exposure assessment are much lower compared to the ones from the exposure assessment (around up to 4-8 times below depending on the population group) performed by the ANS Panel in 2009 (EFSA ANS Panel, 2009) for all population groups. This is due to the fact that in 2012, the Annex II of Regulation (EC) No 1333/2008 was amended as regards the conditions of use and the use levels for Sunset Yellow FCF (E 110) (Commission Regulation (EU) No 232/2012), where MPLs (for which not withdrawn, n=18) were decreased by a factor of 2 to 30. This is also due to a more refined exposure assessment being performed, taking into account the restrictions/exceptions listed in Annex II of Regulation (EC) No 1333/2008, the use of the EFSA Comprehensive Database (FoodEx) system allowing the selection of foods at the level of food items, and excluding the non-relevant food subgroups from the intake calculations.

For children and toddlers, the present exposure estimates were of the same magnitude when compared with the exposure estimates obtained in the refined exposure assessment of Sunset Yellow FCF performed by EFSA in 2011.

Updated information on the actual use levels of Sunset Yellow FCF in foods was made available by the industry for few of the food categories in which this food additive is authorised. However, concentration data on Sunset Yellow FCF in foods provided by Member States were in their majority collected before June 2013 and therefore may not be up-to-date, as mentioned above.

CONCLUSIONS

The newly submitted data from the 28-day toxicity study and the overall available toxicological database on Sunset Yellow, including long-term studies, provides a basis to revise the established temporary ADI. Based on the NOAEL of 375 mg/kg bw/day from the long-term feeding study in rats, and an uncertainty factor of 100, a new ADI for Sunset Yellow FCF of 4 mg/kg bw/day was established by the ANS Panel.

The Panel noted that exposure estimates for Sunset Yellow FCF based both on the currently authorised MPLs and reported use levels provided are well below the new ADI of 4 mg/kg bw/day for all population groups.

Overall, the Panel concluded that, using data provided by the food industry and Member states, the reported uses and use levels of Sunset Yellow FCF (E 110) would not be of safety concern.

DOCUMENTATION PROVIDED TO EFSA

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5. FoodDrinkEurope (FDE). Data on usage levels of Sunset Yellow FCF (E 110). Submitted on 29 November 2013.

6. International Chewing Gum Association (ICGA). Data on usage levels of Sunset Yellow FCF (E 110). Submitted 29 November 2013.

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APPENDICES

Appendix A. Search strategies used for updated extensive literature searches

PubMed

Search strategy on Pubmed Experimental toxicokinetics and toxicodynamic data		
1.	"Sunset yellow FCF" OR "FD and C Yellow No. 6" [Supplementary Concept] OR "C.I. 15-985" OR "sunset yellow" OR "F D and C Yellow #6" OR "gelborange S" OR "C.I. food yellow 3" OR "L-orange 2" OR "orange no.2" OR "E-110"	234
2.	#1 Filters: Publication date from 2008/11/01 to 2013/12/31	77
3.	"toxicity tests"[Mesh] OR "toxicology"[Mesh] OR carcinogenicity[All Fields] OR ("neurotoxicity syndromes"[MeSH Terms] OR ("neurotoxicity"[All Fields] AND "syndromes"[All Fields]) OR "neurotoxicity syndromes"[All Fields] OR "neurotoxicity"[All Fields]) OR immunotoxicity[All Fields] OR "endocrine disruption"[All Fields] OR "Toxic Actions"[Mesh] OR (toxic[All Fields] AND effect[All Fields]) OR (toxic[All Fields] AND effects[All Fields]) OR toxicodynamic[All Fields] OR ("toxicity"[Subheading] OR "toxicity"[All Fields]) OR toxicological[All Fields] OR ("pharmacokinetics"[Subheading] OR "pharmacokinetics"[All Fields] OR "pharmacokinetics"[MeSH Terms]) OR ("pharmacokinetics"[Subheading] OR "pharmacokinetics"[All Fields] OR "toxicokinetics"[All Fields] OR "pharmacokinetics"[MeSH Terms] OR "toxicokinetics"[All Fields]) OR (pharmacodynamic[All Fields] OR pharmacodynamic'[All Fields] OR pharmacodynamical[All Fields] OR pharmacodynamically[All Fields] OR pharmacodynamices[All Fields] OR pharmacodynamicque[All Fields] OR pharmacodynamics[All Fields] OR pharmacodynamics'[All Fields] OR pharmacodynamics,[All Fields]) OR ("behaviour"[All Fields] OR "behavior"[MeSH Terms] OR "behavior"[All Fields]) OR "weight loss"[All Fields] OR "blood changes"[All Fields] OR ("reproduction"[MeSH Terms] OR "reproduction"[All Fields] OR "reproductive"[All Fields]) OR "DNA damages"[All Fields] OR ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) OR ("tumour"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "tumor"[All Fields]) OR genotoxic[All Fields]	6 306 704
4.	#2 AND #3	19

Date of the search: January 13, 2014.

Web of Science

Search strategy on Web of Science Experimental toxicokinetics and toxicodynamic data		
1.	TS=("Sunset yellow FCF" OR “FD and C Yellow No. 6” OR “C.I. 15-985” OR “sunset yellow” OR “F D and C Yellow #6” OR “gelborange S” OR “C.I. food yellow 3” OR “L-orange 2” OR “orange no.2” OR “E-110”)	594
2.	#1 Filters: Publication date from 2008 to 2013	257
3.	TS=("Toxicity Tests" OR “Tests, Toxicity” OR “Test, Toxicity” OR “Toxicity Test” OR "Toxicology" OR "Toxic Actions" OR “Actions, Toxic” OR “toxic effect” OR “toxic effects” OR "toxicity" OR “toxicological” OR “toxicodynamic” OR “toxicodynamical” OR “toxicodynamics” OR “pharmacodynamic*” OR "pharmacokinetics" OR "toxicokinetics" OR “Carcinogenicity” OR “Neurotoxicity” OR “Neurotoxicity Syndrome” OR “Syndrome, Neurotoxicity” OR “Syndromes, Neurotoxicity” OR “Neurotoxic Disorders” OR “Neurotoxic Disorder” OR “Poisoning, Nervous System” OR “Nervous System Poisonings” OR “Poisonings, Nervous System” OR “Nervous System Poisoning” OR “Encephalopathy, Toxic” OR “Encephalopathies, Toxic” OR “Toxic Encephalopathies” OR “Toxic Encephalopathy” OR “Toxic Encephalitis” OR “Encephalitides, Toxic” OR “Encephalitis, Toxic” OR “Toxic Encephalitides” OR “Immunotoxicity” OR "weight loss" OR "blood changes" OR "reproduction" OR "reproductive" OR "endocrine disruption" OR "DNA damages" OR "neoplasms" OR “Neoplasm” OR “Tumors” OR “Tumor” OR “tumour” OR “Neoplasia” OR “Cancer” OR “Cancers” OR “genotoxic*” OR “behavior*” OR “behavior” OR “behaviour”)	4 646 074
4.	#2 AND #3	49

Date of the search: January 13, 2014.

ToxNet

The searches performed in ToxNet on January 13, 2014 did not record additional studies compared to the PubMed and Web of Science databases.

PubMed

Search strategy on Pubmed Human exposure and effect data		
1.	“Sunset yellow FCF” OR “FD and C Yellow No. 6” [Supplementary Concept] OR “C.I. 15-985” OR “sunset yellow” OR “F D and C Yellow #6” OR “gelborange S” OR “C.I. food yellow 3” OR “L-orange 2” OR “orange no.2” OR “E-110”	234
2.	#1 Filters: Publication date from 2008/11/01 to 2013/12/31	77
3.	Biomarkers OR biological markers OR "biological markers"[Mesh] OR Markers, Biological OR Marker, Biological OR Biological Marker OR Biologic Marker OR Marker, Biologic OR Biologic Markers OR Markers, Biologic OR Markers, Clinical OR Clinical Markers OR Marker, Clinical OR Clinical Marker OR Markers, Immunologic OR Marker, Immunologic OR Immune Markers OR Markers, Immune OR Immune Marker OR Marker, Immune OR Immunologic Markers OR Immunologic Marker OR Viral Markers OR Viral Marker OR Marker, Viral OR Markers, Viral OR Serum Markers OR Markers, Serum OR Serum Marker OR Marker, Serum OR Surrogate Endpoints OR Endpoints, Surrogate OR Surrogate End Points OR End Points, Surrogate OR Surrogate Endpoint OR Endpoint, Surrogate OR Surrogate End Point OR End Point, Surrogate OR Surrogate Markers OR Markers, Surrogate OR Surrogate Marker OR Marker, Surrogate OR Biochemical Marker OR Marker, Biochemical OR Markers, Biochemical OR Biochemical Markers OR Markers, Laboratory OR Laboratory Markers OR Marker, Laboratory OR Laboratory Marker	791 187
4.	Epidemiology OR "epidemiology" [Subheading] OR epidemics OR frequency OR surveillance OR morbidity OR occurrence OR outbreaks OR prevalence OR endemics OR incidence OR epidemiologic study OR Epidemiological Studies OR Epidemiological Study OR Studies, Epidemiological OR Study, Epidemiological OR Studies, Epidemiologic OR Epidemiologic Studies OR Study, Epidemiologic	3 850 298

5.	"Case Reports" [Publication Type] OR Case Study OR Case Studies OR case history OR healthy volunteer* OR Case Histories OR “clinical studies” OR “clinical trials” [Publication type]	1 824 104
6.	#3 OR #4 OR #5	6 001 707
7.	#2 AND #6	9
8.	#7 NOT (“Animals” NOT “humans”)	7

Date of the search: January 13, 2014.

Web of Science

Search strategy on Pubmed Human exposure and effect data		
1.	TS=("Sunset yellow FCF" OR “FD and C Yellow No. 6” OR “C.I. 15-985” OR “sunset yellow” OR “F D and C Yellow #6” OR “gelborange S” OR “C.I. food yellow 3” OR “L-orange 2” OR “orange no.2” OR “E-110”)	594
2.	#1 Filters: Publication date from 2008 to 2013	257
3.	TS=(Biomarkers OR biological markers OR "biological markers" OR Markers, Biological OR Marker, Biological OR Biological Marker OR Biologic Marker OR Marker, Biologic OR Biologic Markers OR Markers, Biologic OR Markers, Clinical OR Clinical Markers OR Marker, Clinical OR Clinical Marker OR Markers, Immunologic OR Marker, Immunologic OR Immune Markers OR Markers, Immune OR Immune Marker OR Marker, Immune OR Immunologic Markers OR Immunologic Marker OR Viral Markers OR Viral Marker OR Marker, Viral OR Markers, Viral OR Serum Markers OR Markers, Serum OR Serum Marker OR Marker, Serum OR Surrogate Endpoints OR Endpoints, Surrogate OR Surrogate End Points OR End Points, Surrogate OR Surrogate Endpoint OR Endpoint, Surrogate OR Surrogate End Point OR End Point, Surrogate OR Surrogate Markers OR Markers, Surrogate OR Surrogate Marker OR Marker, Surrogate OR Biochemical Marker OR Marker, Biochemical OR Markers, Biochemical OR Biochemical Markers OR Markers, Laboratory OR Laboratory Markers OR Marker, Laboratory OR Laboratory Marker)	267 619
4.	TS=(Epidemiology OR epidemics OR frequency OR surveillance OR morbidity OR occurrence OR outbreaks OR prevalence OR endemics OR incidence OR epidemiologic study OR Epidemiological Studies OR Epidemiological Study OR Studies, Epidemiological OR Study, Epidemiological OR Studies, Epidemiologic OR Epidemiologic Studies OR Study, Epidemiologic)	2 826 641
5.	TS=("Case Reports" OR Case Study OR Case Studies OR case history OR healthy volunteer* OR Case Histories OR “clinical studies” OR “clinical trials”)	1 399 086
6.	#3 OR #4 OR #5	4 134 605
7.	#2 AND #6	27
8.	#7 NOT TS=(“animals” NOT “humans”)	27

Date of the search: January 13, 2014.

ToxNet

The searches performed in ToxNet on January 13, 2014 did not record additional studies compared to the PubMed and Web of Science databases.

Appendix B. Summary of usage levels reported by industry and analytical data reported by Member States (mg/kg) on Sunset Yellow FCF (E 110)

FCS No	Food category	MPL (mg/l or mg/kg as appropriate)	Restrictions/ exceptions	Reported usage levels							Concentration level from Member States						Data used in the refined scenario
					Maximum reported use levels (mg/l or mg/kg as appropriate)						Positive levels (mg/kg)						
				Total number of data	FDE			ICGA			Number of data	min	median	mean	p95	max	
					n	Typical	Maximum	n	Typical	Maximum							
1.4	**Flavoured fermented milk products including heat treated products**	5															No data/not taken into account
1.6.3	**Other creams**	5	only flavoured creams														No data/ sub food group not in FoodEx
4.2.4.1	**Fruit and vegetable preparations excluding compote**	35	only mostarda di frutta														Not in FoodEx
5.2	**Other confectionery including breath refreshening microsweets**	35	except candied fruit and vegetables; traditional sugar coated nut- or cocoa-based confectionery of almond shape or host shape, typically longer than 2 cm and typically consumed at celebratory occasions, i.e. weddings, communion, etc.								227	0.1	6.2	9.1	30.0	35.0	35
5.2	**Other confectionery including breath refreshening microsweets**	10	only candied fruit and vegetables								5	1.3	5.0	4.8	8.5	8.5	8.5

FCS No	Food category	MPL (mg/l or mg/kg as appropriate)	Restrictions/ exceptions	Reported usage levels							Concentration level from Member States						Data used in the refined scenario
					Maximum reported use levels (mg/l or mg/kg as appropriate)						Positive levels (mg/kg)						
				Total number of data	FDE			ICGA			Number of data	min	median	mean	p95	max	
					n	Typical	Maximum	n	Typical	Maximum							
5.2	**Other confectionery including breath refreshening microsweets**	50	only traditional sugar coated nut- or cocoa-based confectionery of almond shape or host shape, typically longer than 2 cm and typically consumed at celebratory occasions, i.e. weddings, communion, etc.								11	0.2	7.4	10.9	30.5	30.5	30.5
5.3	**Chewing gum**	10		1				1	50	50*	12	0.8	5.4	5.6	10.0	10.0	10
5.4	**Decorations, coatings and fillings, except fruit based fillings covered by category 4.2.4**	35	only decorations, coatings and sauces, except fillings								3	23.8	30.9	29.7	34.4	34.4	Not in FoodEx
5.4	**Decorations, coatings and fillings, except fruit based fillings covered by category 4.2.4**	35	only fillings														Not in FoodEx
6.6	**Batters**	35		1	1	11	11										Not in FoodEx
8.2.1	**Non heat-treated processed meat**	15	only *sobrasada*	1	1	15	15										15
8.2.3	**Casings and coatings and decorations for meat**	35	only decorations and coatings except edible external coating of *pasturmas*	1	1 NP	0.3	0.3										Not in FoodEx
9.2.	**Processed fish and fishery products including mollusks and crustaceans**	200	only in salmon substitutes based on *Theragra chalcogramma*								69	46.0	113.1	120.4	195.0	198.4	198.4

FCS No	Food category	MPL (mg/l or mg/kg as appropriate)	Restrictions/ exceptions	Reported usage levels							Concentration level from Member States						Data used in the refined scenario
					Maximum reported use levels (mg/l or mg/kg as appropriate)						Positive levels (mg/kg)						
				Total number of data	FDE			ICGA			Number of data	min	median	mean	p95	max	
					n	Typical	Maximum	n	Typical	Maximum							
			and *Pollachius virens*														
9.3	**Fish roe**	200	except Sturgeons' eggs (Caviar)								15	8.0	88.0	83.7	122.0	122.0	122.0
12.4	**Mustard**	50									1	8.3	8.3	8.3	8.3	8.3	8.3
12.6	**Sauces**	30	only in pickles and piccalilli	1	1	17	20				1	12.7	12.7	12.7	12.7	12.7	20.0
12.9	**Protein products, excluding products covered in category 1.8**	20	only meat and fish analogues based on vegetable proteins														No data/not taken into account
13.2	**Dietary foods for special medical purposes defined in Directive 1999/21/EC (excluding products from food category 13.1.5)**	10															No data/not taken into account
13.3	**Dietary foods for weight control diets intended to replace total daily food intake or an individual meal (the whole or part of the total daily diet)**	10															No data/not taken into account
14.1.4	**Flavoured drinks**	20	excluding chocolate milk and malt products	31	31	10	20				147	0.2	5.1	6.4	16.0	19.3	20.0
14.2.3	**Cider and perry**	10	excluding *cidre bouché*														No data/not taken into account
14.2.4	**Fruit wine and made wine**	10	-														No data/not taken

FCS No	Food category	MPL (mg/l or mg/kg as appropriate)	Restrictions/ exceptions	Reported usage levels							Concentration level from Member States						Data used in the refined scenario
					Maximum reported use levels (mg/l or mg/kg as appropriate)						Positive levels (mg/kg)						
				Total number of data	FDE			ICGA			Number of data	min	median	mean	p95	max	
					n	Typical	Maximum	n	Typical	Maximum							
																	into account
14.2.6	**Spirit drinks as defined in Regulation (EC) No 110/2008**	100	except: spirit drinks as defined in Article 5(1) and sales denominations listed in Annex II, paragraphs 1-14 of Regulation (EC) No 110/2008 and spirits (preceded by the name of the fruit) obtained by maceration and distillation, Geist (with the name of the fruit or the raw material used), London Gin, Sambuca, Maraschino, Marrasquino or Maraskino and Mistrà								12	0.2	1.9	7.3	33.6	33.6	33.6
14.2.7.1	**Aromatised wines**	50	except *americano, bitter vino*														23.0
14.2.7.1	**Aromatised wines**	50	only *bitter vino*														
14.2.7.2	**Aromatised wine-based drinks**	50	except *bitter soda, sangria, claria, zurra*														
14.2.7.2	**Aromatised wine-based drinks**	50	only *bitter soda*														
14.2.7.3	**Aromatised wine-product cocktails**	50									3	8.6	21.7	17.8	23.0	23.0	

FCS No	Food category	MPL (mg/l or mg/kg as appropriate)	Restrictions/ exceptions	Reported usage levels							Concentration level from Member States						Data used in the refined scenario
					Maximum reported use levels (mg/l or mg/kg as appropriate)						Positive levels (mg/kg)						
				Total number of data	FDE			ICGA			Number of data	min	median	mean	p95	max	
					n	Typical	Maximum	n	Typical	Maximum							
14.2.8	**Alcoholic beverages, including alcohol-free and low-alcohol counterparts**	100	only alcoholic drinks with less than 15 % of alcohol								70	0.4	4.1	6.8	22.7	37.8	37.8
16	**Desserts excluding products covered in category 1, 3 and 4**	5									2	2.0	3.2	3.2	4.3	4.3	4.3
17.1	**Food supplements supplied in a solid form including capsules and tablets and similar forms excluding chewable forms**	10															No data/not taken into account
17.2	**Food supplements supplied in a liquid form**	10															
17.3	**Food supplements supplied in a syrup-type or chewable form**	10															

(a): This information had been collected in the course of 2012 and the value provided resulted to be above the MPL currently authorised for Sunset Yellow FCF in chewing gum.

Summary of total estimated exposure to Sunset Yellow FCF (E 110) using MPLs and reported use levels per age class and survey: mean and high level (mg/kg bw/day)

	Number of subjects	MPL		Reported use levels	
		Mean	High level	Mean	High level
Toddlers					
Belgium (Regional_Flanders)	36	0.37	-	0.33	-
Bulgaria (NUTRICHILD)	428	0.05	0.25	0.05	0.25
Germany (DONALD_2006_2008)	261	0.05	0.23	0.04	0.21
Spain (enKid)	17	0.03	-	0.01	-
Finland (DIPP_2003_2006)	497	0.04	0.12	0.01	0.02
Italy (INRAN_SCAI_2005_06)	36	0.02	-	0.01	-
Netherlands (VCP_kids)	322	0.19	0.61	0.15	0.61
Children					
Belgium (Regional_Flanders)	625	0.29	0.76	0.26	0.72
Bulgaria (NUTRICHILD)	433	0.10	0.39	0.10	0.39
Czech Republic (SISP04)	389	0.13	0.51	0.12	0.51
Germany (DONALD_2006_2008)	660	0.15	0.48	0.14	0.47
Denmark (Danish_Dietary_Survey)	490	0.19	0.42	0.18	0.41
Spain (enKid)	156	0.07	0.31	0.06	0.29
Spain (NUT_INK05)	399	0.06	0.22	0.05	0.21
Finland (DIPP_2003_2006)	933	0.09	0.27	0.07	0.25
Finland (STRIP)	250	0.14	0.36	0.13	0.35
France (INCA2)	482	0.08	0.28	0.07	0.26
Greece (Regional_Crete)	839	0.03	0.13	0.03	0.13
Italy (INRAN_SCAI_2005_06)	193	0.03	0.11	0.02	0.11
Latvia (EFSA_TEST)	189	0.06	0.25	0.06	0.25
Netherlands (VCP_kids)	957	0.19	0.55	0.16	0.50
Sweden (NFA)	1473	0.26	0.58	0.24	0.56
Adolescents					
Belgium (Diet_National_2004)	584	0.15	0.45	0.15	0.42
Cyprus (Childhealth)	303	0.03	0.12	0.03	0.11
Czech Republic (SISP04)	298	0.12	0.39	0.11	0.37
Germany (National_Nutrition_Survey_II)	1011	0.08	0.35	0.07	0.31
Denmark (Danish_Dietary_Survey)	479	0.16	0.39	0.15	0.38
Spain (AESAN_FIAB)	86	0.03	0.16	0.03	0.16
Spain (enKid)	209	0.05	0.22	0.05	0.21
Spain (NUT_INK05)	651	0.06	0.20	0.05	0.19
France (INCA2)	973	0.05	0.17	0.04	0.16
Italy (INRAN_SCAI_2005_06)	247	0.03	0.12	0.03	0.12
Latvia (EFSA_TEST)	470	0.04	0.17	0.04	0.16
Sweden (NFA)	1018	0.17	0.39	0.16	0.38

	Number of subjects	MPL		Reported use levels	
		Mean	High level	Mean	High level
Adults					
Belgium (Diet_National_2004)	1304	0.10	0.37	0.09	0.34
Czech Republic (SISP04)	1666	0.04	0.18	0.03	0.17
Germany (National_Nutrition_Survey_II)	10419	0.04	0.21	0.04	0.19
Denmark (Danish_Dietary_Survey)	2822	0.07	0.21	0.06	0.20
Spain (AESAN)	410	0.04	0.16	0.04	0.16
Spain (AESAN_FIAB)	981	0.03	0.13	0.03	0.12
Finland (FINDIET_2007)	1575	0.03	0.14	0.02	0.11
France (INCA2)	2276	0.04	0.16	0.03	0.12
United Kingdom (NDNS)	1724	0.07	0.24	0.05	0.18
Hungary (National_Repr_Surv)	1074	0.04	0.15	0.04	0.15
Ireland (NSIFCS)	958	0.06	0.21	0.04	0.16
Italy (INRAN_SCAI_2005_06)	2313	0.01	0.06	0.01	0.05
Latvia (EFSA_TEST)	1306	0.02	0.10	0.02	0.08
Netherlands (DNFCS_2003)	750	0.13	0.37	0.12	0.36
Sweden (Riksmaten_1997_98)	1210	0.06	0.21	0.06	0.19
The Elderly					
Belgium (Diet_National_2004)	1230	0.03	0.12	0.02	0.11
Germany (National_Nutrition_Survey_II)	2496	0.01	0.06	0.01	0.05
Denmark (Danish_Dietary_Survey)	329	0.03	0.11	0.02	0.09
Finland (FINDIET_2007)	463	0.01	0.06	0.01	0.04
France (INCA2)	348	0.01	0.06	0.01	0.03
Hungary (National_Repr_Surv)	286	0.03	0.09	0.02	0.09
Italy (INRAN_SCAI_2005_06)	518	0.00	0.02	0.00	0.02

Note: The different methodologies of European dietary surveys included in the EFSA Comprehensive Database are fully described in the Guidance on the use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment (EFSA, 2011b). A summary is available p.11, Table 1 of the guidance.

GLOSSARY AND ABBREVIATIONS

ADI	Acceptable Daily Intake
tADI	temporary ADI
AFSSA	Agence Française de Sécurité Sanitaire des Aliments
ANS Panel	Scientific Panel on Food Additives and Nutrient Sources added to Food
ANSES	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail
bw	Body weight
CCMA	Certified Color Manufacturers Association
CEPS	European Spirits Organisation
CIAA	Confederation of the Food and Drink Industries of the EU
EC	European Commission
EFSA	European Food Safety Authority
ELC	Federation of European Food Additives, Food Enzymes and Food Culture Industries
ER	Oestrogen receptor
EU	European Union
EXPOCHI	Individual food consumption data and exposure assessment studies for children
FAO	Food and Agricultural Organisation
FCS	Food Categorisation System (food nomenclature) presented in the Annex II of Regulation (EC) No 1333/2008
FDA	United States Food and Drug Administration
FDE	FoodDrinkEurope
FSA	UK Food Standards Agency
FSAI	Food Safety Authority of Ireland
GLP	Good Laboratory Practice
i.p.	intraperitoneal
JECFA	Joint FAO/WHO Expert Committee on Food Additives
ICGA	International Chewing Gum Association
LOD	Limit of detection
MLR	Mixed Lymphocyte Reaction
MPL	Maximum Permitted Level
MS	Member States
MTD	maximum tolerated dose
nAChRs	nicotinic acetylcholine receptors
NMDAR	N-methyl-D-aspartate receptors
NOAEL	No-Observed-Adverse-Effect Level

NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
PI	Propidium Iodide
SCF	Scientific Committee for Food
SCOOP	A scientific cooperation (SCOOP) task involves coordination amongst Member States to provide pooled data from across the EU on particular issues of concern regarding food safety
TA	transcriptional activation
UK	United Kingdom
UNESDA	Union of European Soft Drinks Associations
WHO	World Health Organization