



Nederlandse Voedsel- en
Warenautoriteit
*Ministerie van Landbouw,
Natuur en Voedselkwaliteit*



Titanium dioxide: Regulatory and risk assessment aspects from a food perspective

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NVWA, Office for Risk
Assessment and Research



Outline

NVWA, Office for Risk
Assessment and Research

Regulations

EFSA: history of risk
assessments

Updated, recent risk
assessment



Office for Risk Assessment & Research

Mission

To assess risks in the remit of the NVWA domains and provide advice/opinions



Tasks

1. Independent scientific risk assessment and advice
 2. Programming and co-ordination of research
 3. Support of inspection policy
- › The law on independent risk assessment (2006)





Advice BuR(O), 2007/2008

- Promote research into safety of foods that contain nanoparticles
- Consider foods with (engineered) nanoparticles as novel foods

Datum 29 september 2010
Betreft Informatie over nanosilicadeeltjes ... levensmiddelen

Geachte heer Schreuders,

Deze brief is bedoeld om de departementen van VWS en LNV, en de nVWA, te informeren over de eerste resultaten van onderzoek naar de veiligheid van nanosilicadeeltjes. Dit onderzoek vloeit voort uit de aandacht voor de mogelijke risico's van nanodeeltjes voor mens en milieu zoals die door het huidige kabinet wordt gewenst.

Samenvatting

Toepassingen van nanotechnologie in voedings- en verpakkingsmiddelen lijken een grote vlucht te gaan nemen. Voordat nanodeeltjes op grote schaal worden toegepast is het belangrijk om inzicht te krijgen in mogelijke nadelige gezondheidseffecten van deze toepassingen. Kennis ontbreekt over wat de gevolgen zijn van nano-afmetingen voor de toxicokinetiek en toxicodynamiek van stoffen. Met name voor de bewust geproduceerde deeltjes die niet oplosbaar of afbreekbaar zijn, is er reden tot bezorgdheid. Om de veiligheid van nanodeeltjes te kunnen beoordelen, moet kennis worden gegenereerd over fysisch-chemische eigenschappen, zoals deeltjesgrootte, vorm, oppervlakte-eigenschappen en dergelijke die van invloed kunnen zijn op de toxiciteit. Bovendien moeten hiertoe, en voor wetgeving, standaard dosismeeteenheden worden gedefinieerd.

Bureau Risicobeoordeling adviseert:

1. onderzoek te stimuleren naar de veiligheid van voedsel dat nanodeeltjes bevat, waar mogelijk in internationale afstemming. Dit onderzoek vraagt om een investering in:
 - a. meetmethoden en meetapparatuur;
 - b. onderzoek naar kennislacunes: blootstelling, opname, verdeling en effecten van nanodeeltjes;
2. voedingsmiddelen of voedsel ingrediënten die (bewust geproduceerde) nanodeeltjes bevatten als 'nieuw' te beschouwen zodat de Verordening inzake nieuwe voedingsmiddelen en nieuwe voedsel ingrediënten (EC/258/97) van toepassing is;
3. de veiligheid van additieven en aroma's die nanodeeltjes bevatten te beoordelen ook als het gaat om nanoformuleringen van eerder toegelaten producten.

datum
29 januari 2008
oms kenmerk
VWA/BuR2007/54281

pagina
1 / 12

behandeld door



Titanium dioxide in food



- › Titanium dioxide (TiO_2) is a food additive used to enhance the white colour and brightness
- › Food additive E171
- › White colour because of particles 200-300 nm; part of TiO_2 particles <100 nm
- › Applied in, amongst others:
 - candy, chewing gum, pastries, creamer
 - food supplements
 - toothpaste (CI 77891)





General Food Law Regulation (EC) No 178/2002

FBOs (food/feed businesses) are primarily **responsible** for the safety of their products

In order for there to be confidence in the scientific basis for food law, **risk assessments** should be undertaken in an **independent, objective and transparent** manner, on the basis of the available **scientific information and data**

Regulation (EC) No 1333/2008 on **food additives**. Only food additives that are included in the Union list may be placed on the market and used in foods under the specified conditions of use



Regulatory framework TiO₂

- › Titanium dioxide (E171): authorised as a food additive in the EU according to Regulation (EC) No 1333/2008
- › Specifications defined in Commission Regulation (EU) No 231/2012
- › Since E171 was permitted in the Union before 20 January 2009: food additives are subjected to a new risk assessment by EFSA (Commission Regulation (EU) No 257/2010 and in line with Regulation (EC) No 1333/2008)
- › Definition in Regulation (EU) No 231/2012: Titanium dioxide consists essentially of pure anatase and/or rutile titanium dioxide which may be coated with small amounts of alumina and/or silica to improve the technological properties of the product. The anatase grades of pigmentary titanium dioxide can only be made by the sulphate process which creates a large amount of sulphuric acid as a by-product. The rutile grades of titanium dioxide are typically made by the chloride process....



BuRO and nanoparticles

- Beginning 2008: BuRO advice
- July 2013: international workshop on nano silica
- Several P9 and WOT projects – chemical analyses and risk assessment
- Characterization of titanium dioxide nanoparticles in food products: analytical methods to define nanoparticles (Peters RJ et al., J Agric Food Chem 2014;62(27):6285-93)
- Oral intake of added TiO_2 and its nanofraction from food products, food supplements and tooth paste by the Dutch population (Rompelberg et al., Nanotechnology 2016;10(10):1404-14)
- Risk assessment of titanium dioxide nanoparticles via oral exposure, including toxicokinetic considerations (Heringa et al., Nanotoxicology 2016;10(10):1515-25)

Characterization of Titanium Dioxide Nanoparticles in Food Products: Analytical Methods To Define Nanoparticles
Ruud J. B. Peters[†], Greet van Bommel[†], Zahra Herrera-Rivera[†], Hans P. F. G. Heijer[†], Hans J. P. Marvin[†], Stefan Weigel[†], Peter C. Tromp[§], Agnes G. Oomen[†], Anton G. Rietveld[†], and Hans Bouwmeester[†]

View Author Information

Cite this: J. Agric. Food Chem. 2014, 62, 27, 6285-6293



Oral intake of added titanium dioxide and its nanofraction from food products, food supplements and toothpaste by the Dutch population

Cathy Rompelberg, Minne B. Heringa, Gerda van Donkersgoed, José Drijvers, Agnes Roos, Susanne Westenbrink, Ruud Peters, Greet van Bommel, Walter Brand & Agnes G. Oomen



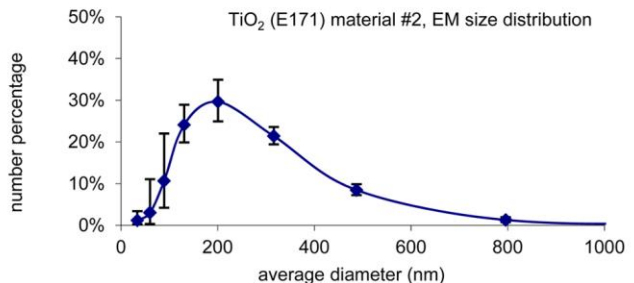
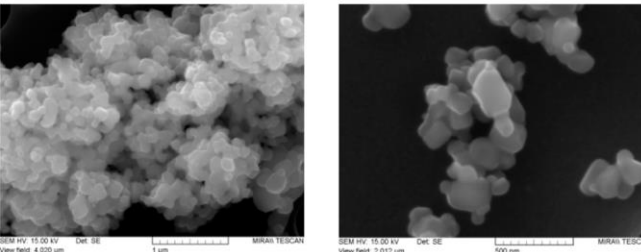
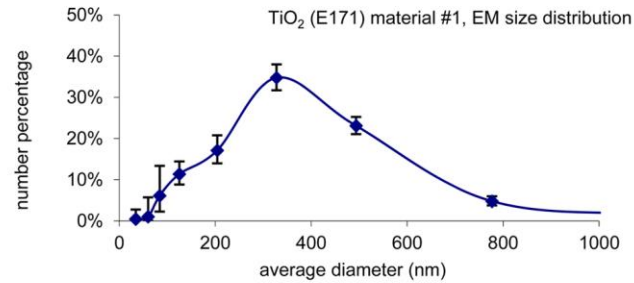
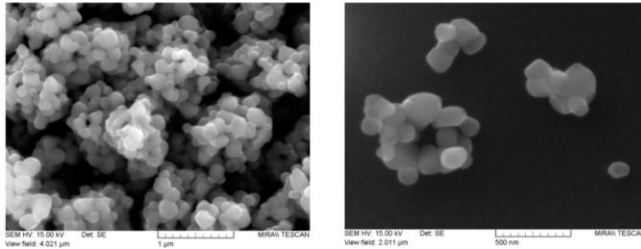
Risk assessment of titanium dioxide nanoparticles via oral exposure, including toxicokinetic considerations

Minne B. Heringa, Liesbeth Geraets, Jan C. H. van Eijkeren, Rob J. Vandebruiel, Wim H. de Jong & Agnes G. Oomen



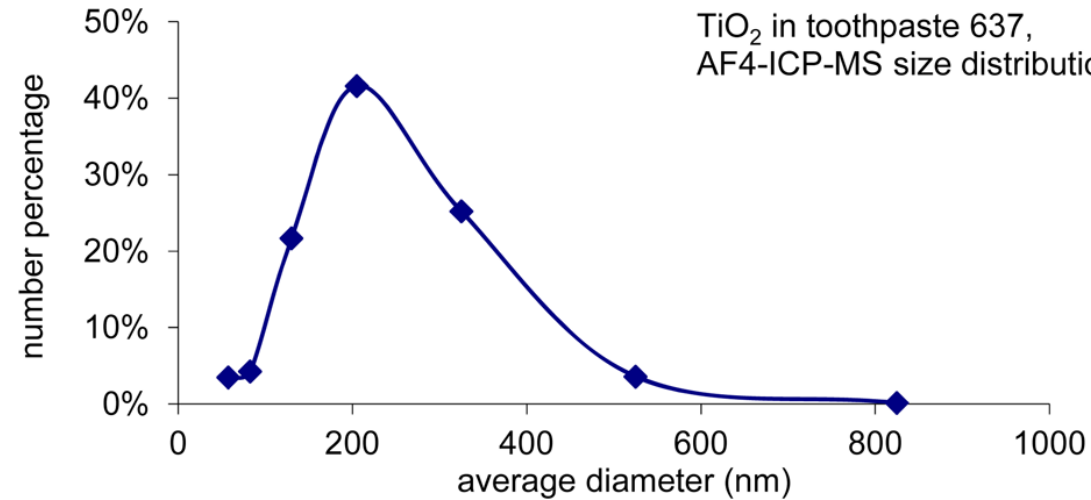
RIKILT (WFSR): size distribution

E171:

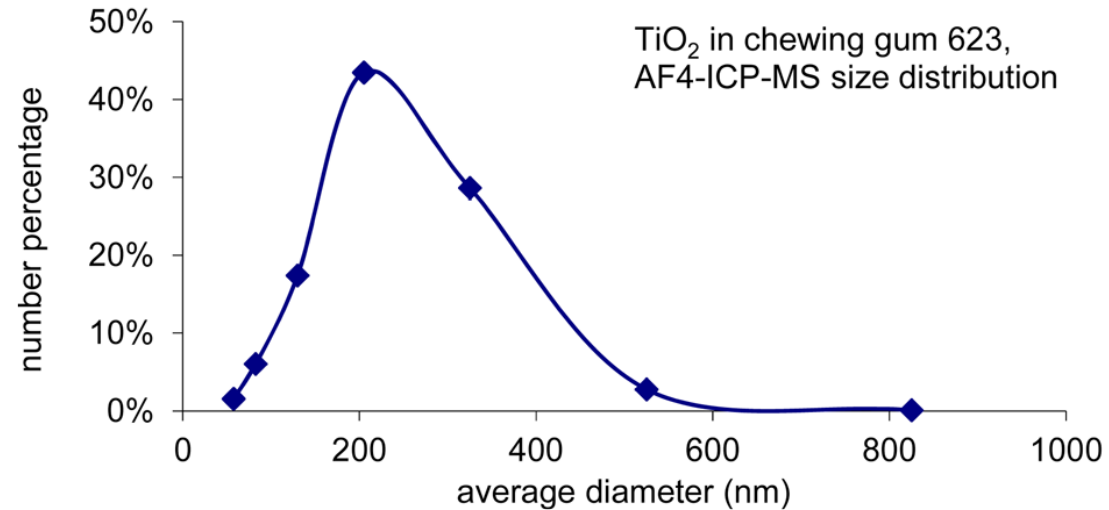


Products:

TiO₂ in toothpaste 637,
AF4-ICP-MS size distribution



TiO₂ in chewing gum 623,
AF4-ICP-MS size distribution



Conclusion:
5-12% of the
TiO₂ particles
in these
materials and
products was
<100 nm



Estimated intakes and main food sources

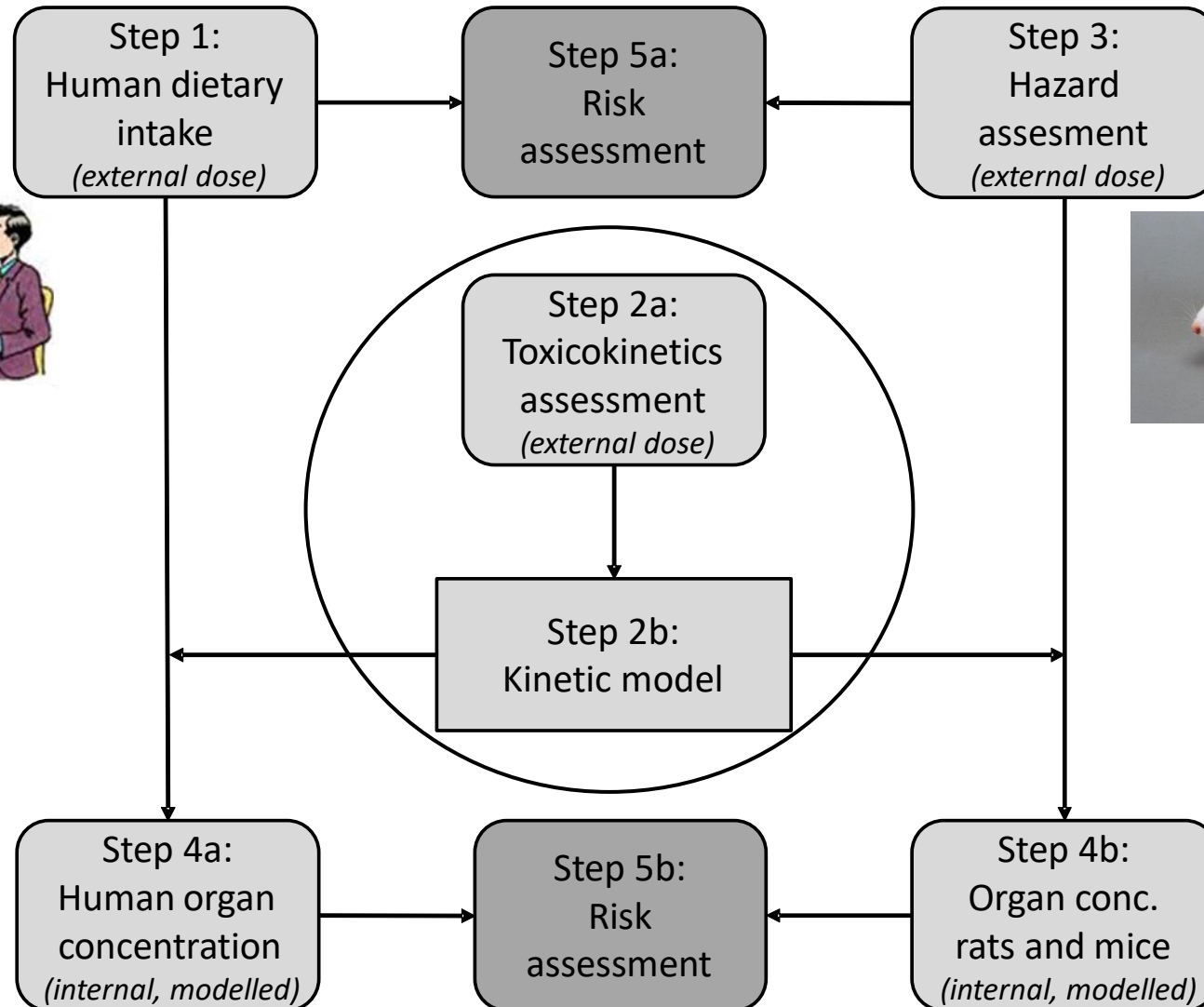
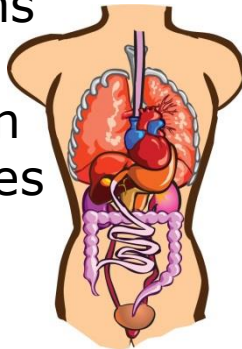
P95, mg/kg bw/d	TiO ₂		TiO ₂ NP		
	2-6 y	lifelong	2-6 y	lifelong	
RIVM, 2016	1.29	0.52	0.00416	0.000167	0.31% (by mass) fraction (<100 nm)
EFSA, non-brand loyal scenario, 2016	0.5-14.8		0.02-0.47		excl. toothpaste

Top ten	DNFCS-Children (2-6 y old)	DNFCS-2007-2010 (7-69 y old)	DNFCS-older adults (70+)
1	Tooth paste (57%)	Chewing gum (14%)	Coffee creamer (13%)
2	Hard candy with sugar (4%)	Coffee creamer (11%)	Thickened milk for coffee, powdered (8%)
3	Sugar-coated chocolate confectionery (3%)	Mayonnaise normal (7%)	Chewing gum (4%)
4	Chewing gum with sugar (2%)	Sauce, garlic, mayonnaise based (5%)	Cappuccino with caffeine (3%)
5	Sugar-coated chocolates (2%)	Cappuccino (4%)	Cappuccino instant ready to drink (3%)



RIVM approach for risk assessment

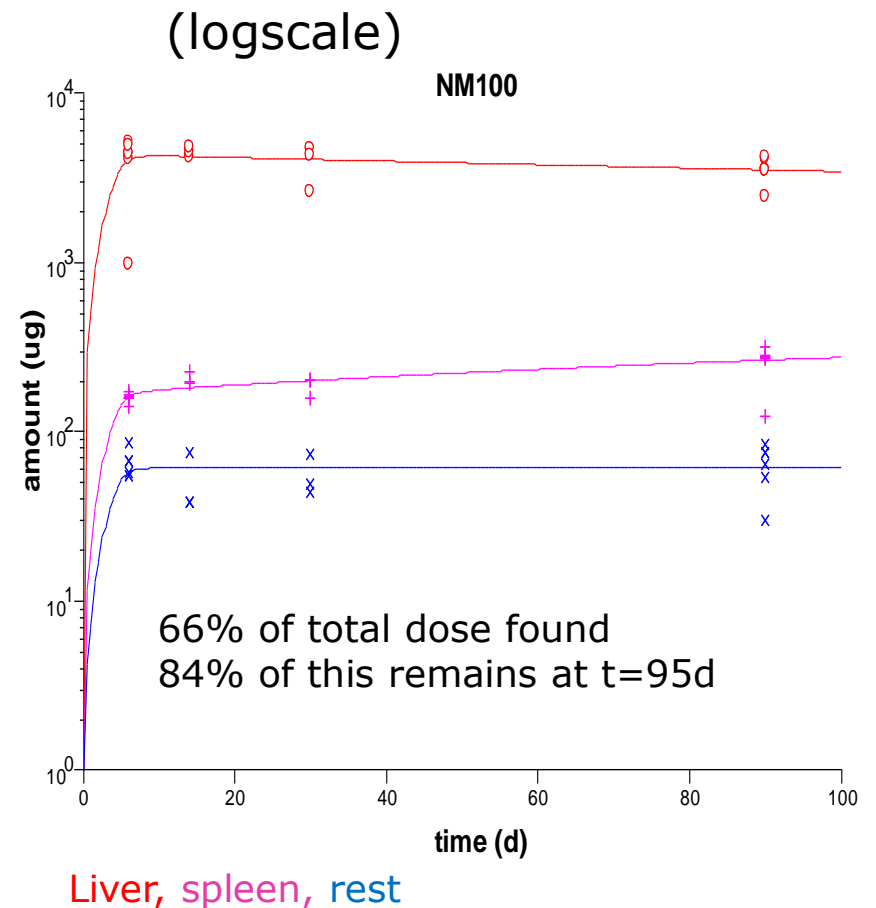
Approach 2:
Margins between
estimated tissue
concentrations in
humans and
the (no) effect
concentrations
in tissues
obtained from
toxicity studies
in rodents





Toxicokinetic model, conclusions TiO_2

- Oral study: very low absorption: 0.02%
- Highest levels in liver and spleen, half life 28-650 d
- Some elimination from liver, none from spleen → accumulation
- None of the key toxicity studies (oral, iv) was ideal. Nice fit to data
- Rutile forms gave ~factor 4 higher spleen concentrations than anatase





Risk assessment

- › Traditional approach: based on key studies with rats and mice: MOEs ranging from <150-1500
 - Human health risk cannot be excluded for effects on thyroid gland, ovaries, thyroid hormone balance, spleen, kidneys and testes
- › Toxicokinetic approach: MOSs ranging from 8.1-210 for animal studies (liver):
 - Human health risk cannot be excluded for effects on liver
 - Important to include toxicokinetics as this changes risk assessment outcome for this accumulating substance





What are the real organ levels in humans? (did we estimate them correctly?)

- > TiO₂ particle concentration in post-mortem human liver and spleen analysed

- Age, gender, ethnicity

Heringa et al. *Particle and Fibre Toxicology* (2018) 15:15
<https://doi.org/10.1186/s12989-018-0251-7>

Particle and Fibre Toxicology

RESEARCH

Open Access

Detection of titanium particles in human liver and spleen and possible health implications

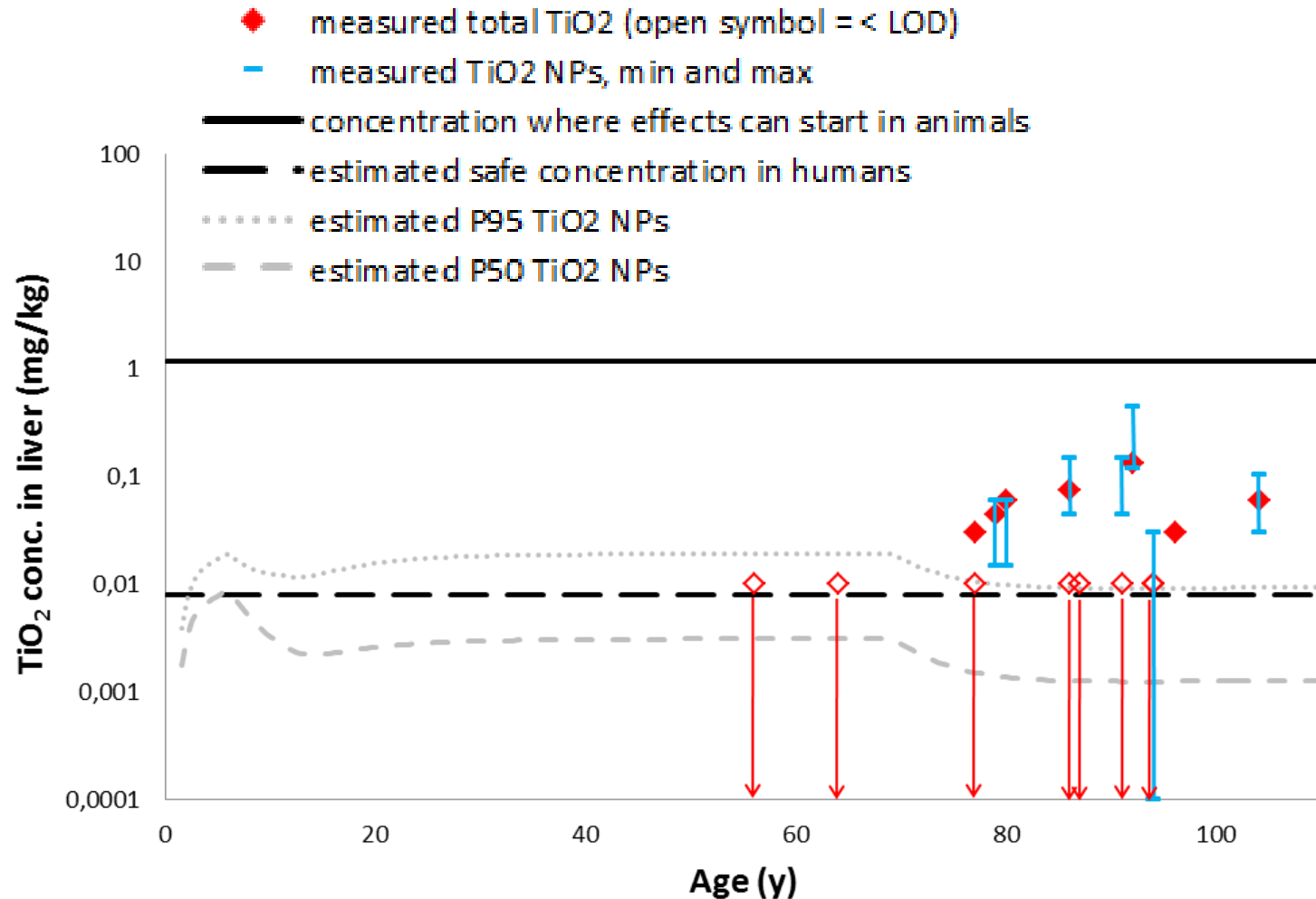


M. B. Heringa^{1*}, R. J. B. Peters², R. L. A. W. Bleys³, M. K. van der Lee², P. C. Tromp⁴, P. C. E. van Kesteren¹, J. C. H. van Eijkeren¹, A. K. Undas², A. G. Oomen¹ and H. Bouwmeester^{2,5}

- > Method for Ti and TiO₂ analysis validated (by RIKILT)



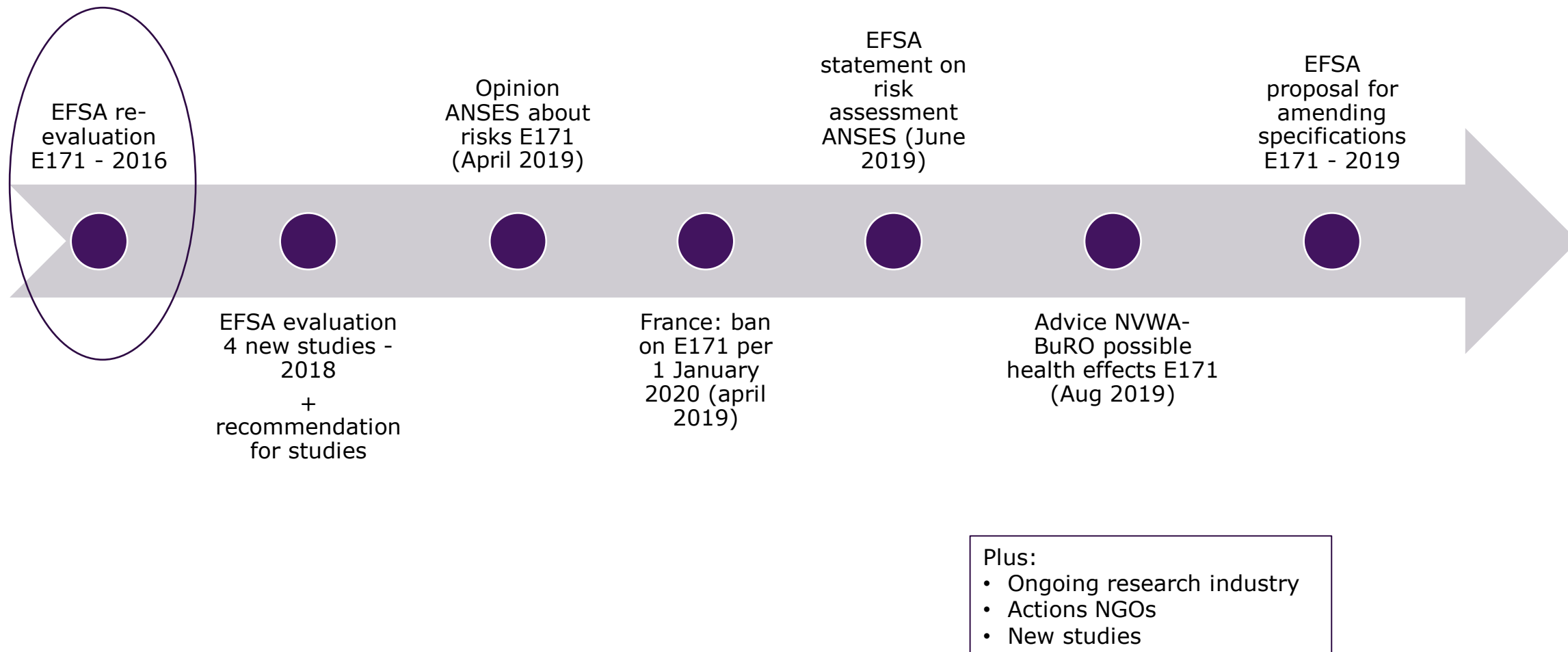
Comparison to model predictions: liver



- > Size range particles in organs within range of particles in food products (30-600 nm diameter)
- > It can be assumed that these levels come from oral exposure
- > Liver Ti/TiO₂ concentrations in humans are below the liver concentrations related to adverse effects in toxicity studies. However, the MoE is limited, thus **risk cannot be excluded**



Timeline risk assessment E171 by EFSA





Previous risk assessments of TiO₂

- TiO₂ used in Europa for decades as food additive
 - 1969/1970: JECFA no limit on the intake of TiO₂ (insoluble and inert) (anatase and rutile forms not distinguished)
 - 1975: SCF no ADI for TiO₂ (use of this colouring matter for the surface and colouring of sugar confectionery only)
 - 1977: SCF: new information on other uses (colours for which an ADI was not established but which could be used in food)
- ADI not necessary due to insolubility, low absorption, no indication of accumulation; NCI study showed no effects; *quantum satis* (as much as needed)
- 2005: EFSA Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC Panel): rutile and anatase TiO₂ same bioavailability and thus toxicological database applicable to either form

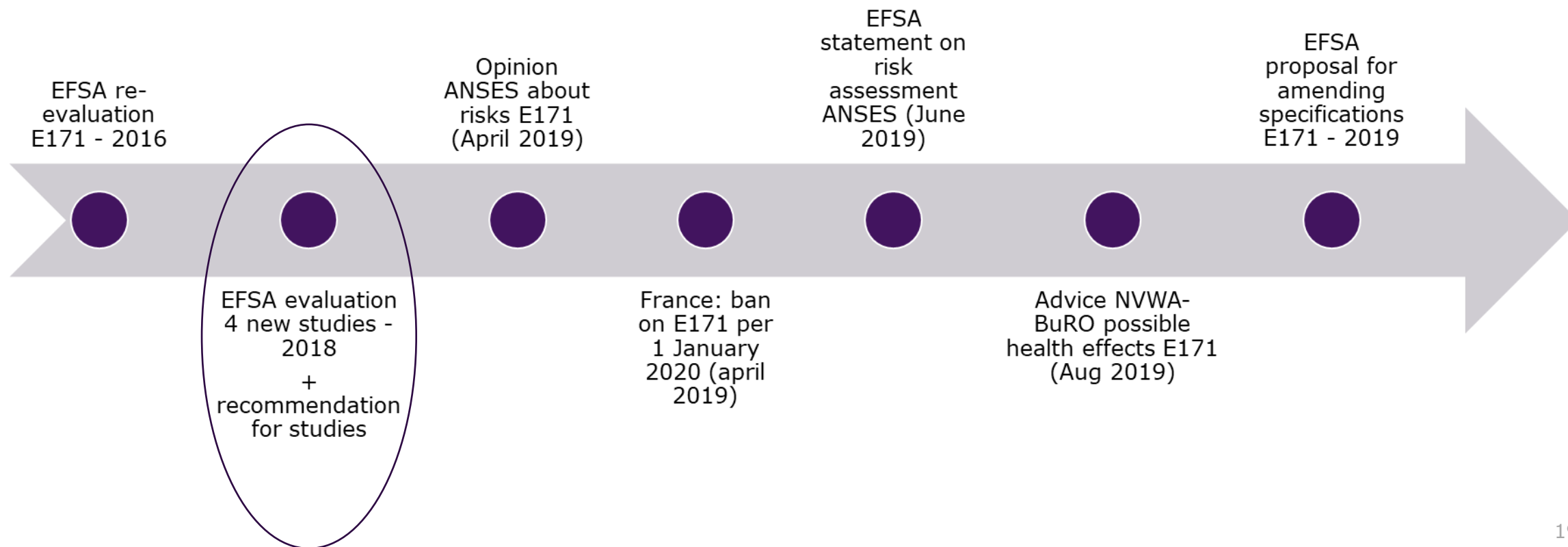


EFSA re-evaluation, 2016

- EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS Panel) re-evaluated safety of TiO_2
- No concerns with respect to genotoxicity and carcinogenicity, but unable to establish a health-based guidance value (HBGV) (gaps in dataset: reprotox and characterization of material)
- Panel considered that 'E171 mainly consisted of micro-sized TiO_2 particles, with a nano-sized (<100 nm) fraction less than 3.2% by mass'
- Request for extended one-generation reproductive toxicity study (EOGRTS)
- Panel concluded that, based on a margin of safety (MoS) calculated from the no-observed-adverse-effect level (NOAEL) of 2,250 mg TiO_2 /kg bw per day (identified from a carcinogenicity study in rats) and the exposure, E171 would not be of concern
- January 2017: Call by EC to interested business operators (IBOs): data on the characterisation of the material and the performance of a new extended one-generation reproductive toxicity study (EOGRTS) in rodents



Timeline risk assessment E171





EFSA evaluation of 4 studies

- Bettini et al. (2017). Food-grade TiO_2 impairs intestinal and systemic immune homeostasis, initiates preneoplastic lesions and promotes aberrant crypt development in the rat colon. *Sci Rep* 2017;7:40373.
 - Guo et al. (2017). Titanium dioxide nanoparticle ingestion alters nutrient absorption in an in vitro model of the small intestine. *Nano Impact* 20-17;5:70-82
 - Heringa et al. (2016). Risk assessment of titanium dioxide nanoparticles via oral exposure, including toxicokinetic considerations. *Nanotoxicology* 2016;10
 - Proquin et al. (2016). Titanium dioxide food additive (E171) induces ROS formation and genotoxicity: contribution of micro and nano-sized fractions. *Mutagenesis* 2017;32:139–149
-
- Bettini et al. (2017): indications development colon cancer in rats
 - Guo et al. (2016): absorption changed *in vitro*
 - Heringa et al. (2016): possible effects on liver
 - Proquin et al. (2017): mechanism cancer of intestine

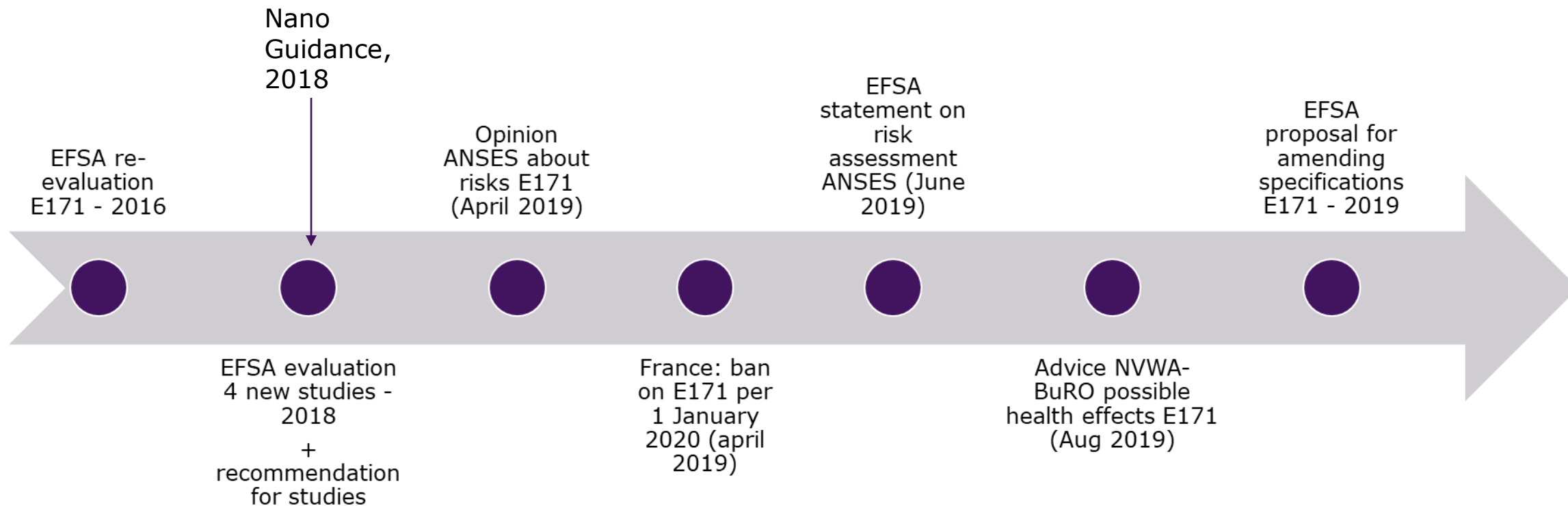


Conclusion EFSA ANS Panel

- EFSA considered studies in context of the conclusions of EFSA opinion of 2016
- The four studies highlighted some concerns but with uncertainties, therefore their relevance for the risk assessment was considered limited and further research would be needed to decrease the level of uncertainties
- Altogether, the Panel concluded that the outcome of the four studies *did not merit re-opening the existing opinion of EFSA related to the safety of titanium dioxide (E171) as a food additive*
- ... but recommended the inclusion of biomarkers for putative pre-cancerous lesions in the colon to be included in the ongoing EOGRTS as additional parameters to be investigated and further studies on TiO₂ NP should include administration in a food matrix



Timeline risk assessment E171



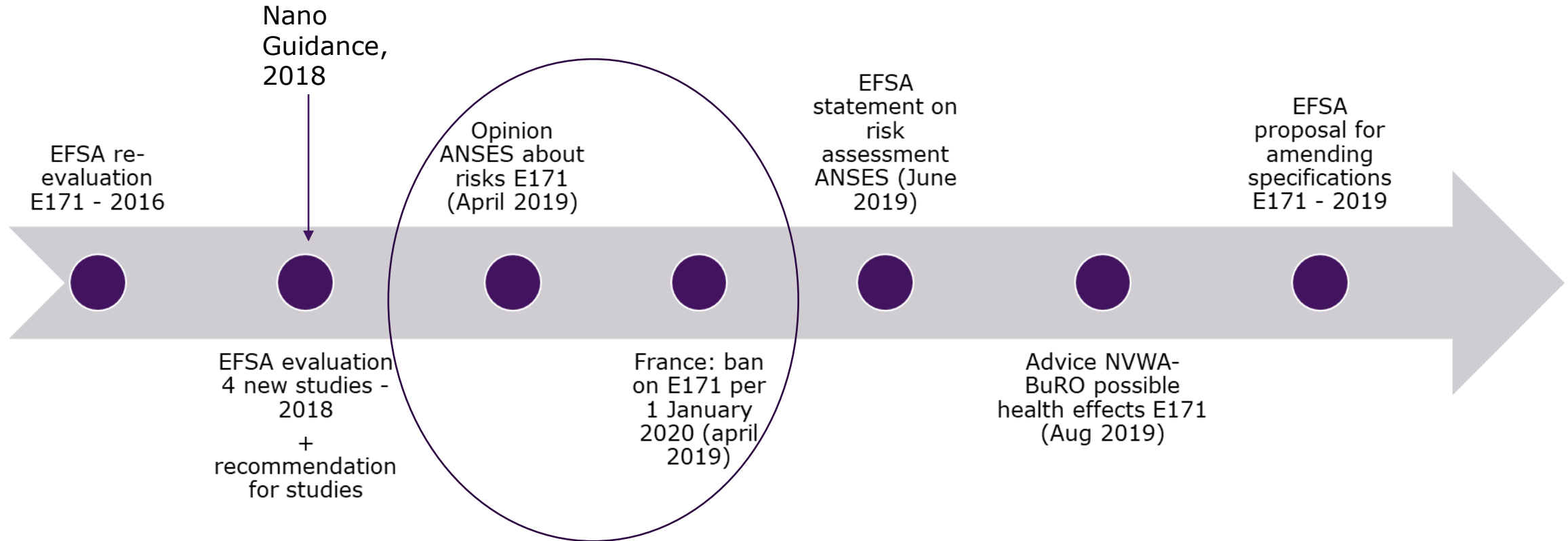


Nano Guidance

- In July 2018, EFSA SC published a Guidance on risk assessment of the application of nanoscience and nanotechnologies in the food and feed chain: Part 1, human and animal health
- Updating the 2011 Guidance and clarifying that conventional materials containing a fraction of nanoparticles require specific risk assessment considerations



Timeline risk assessment E171





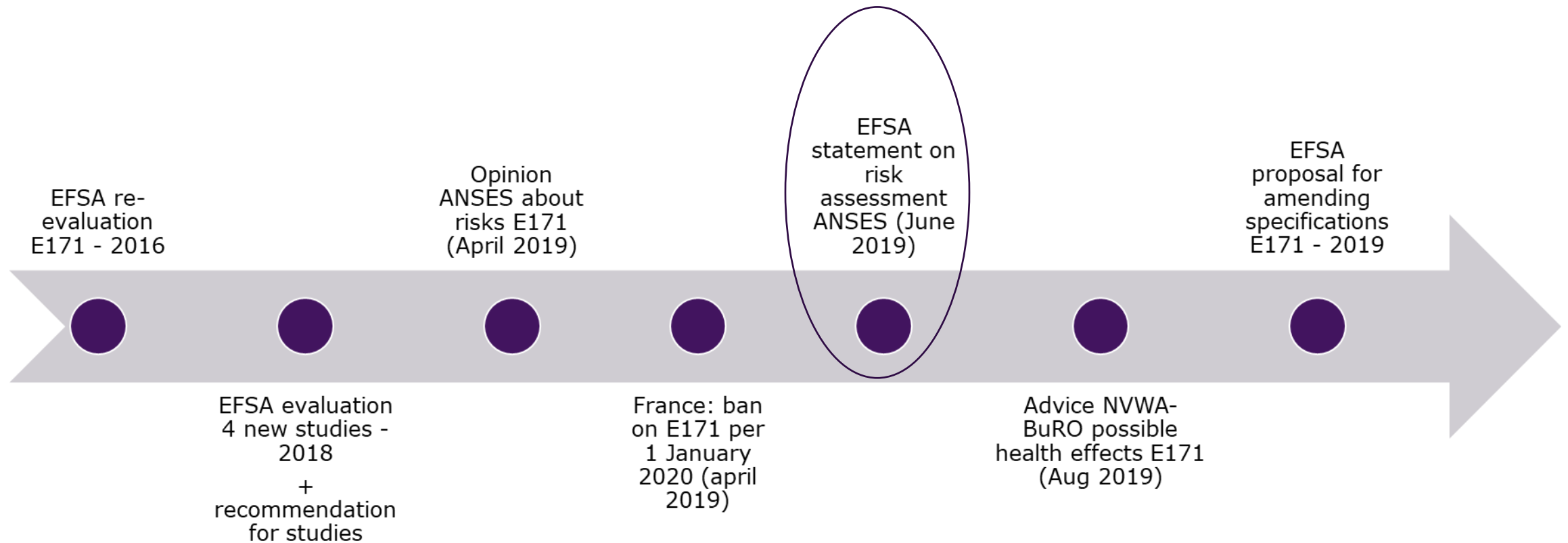
ANSES, France

- 12 April 2019: Opinion of the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) on the risks associated with ingestion of the food additive E171
 - 25 new studies (2017-2019) identified
 - No studies confirmed carcinogenesis-promoting effect of E171
 - ANSES reiterated its 2017 conclusions
 - Great heterogeneity of E171 batches produced and placed on the market
 - Better characterising the hazard: reprotoxicity and *in vivo* genotoxicity studies
 - Assessing justification for use for the consumer, based on clearly established benefits (technological value, substitution impossible, value to the consumer/community)
- April 2019: French Government introduced ban on foods containing the additive E171. French decree entered into force on 1 January 2020, was based on the application of the precautionary principle. Ban reconfirmed for 2021, pending the finalisation of the assessment by EFSA





Timeline risk assessments E171





NGOs

- > Several NGOs active
- > Petition to EU to ban E171 (May 2019)
- > Supporting French measure
- > Measurements of particle size distribution in products containing E171
- > Addressing manufacturers



Vice-President Jyrki Katainen
European Commission
Rue de la Loi 200
B – 1049 Brussels

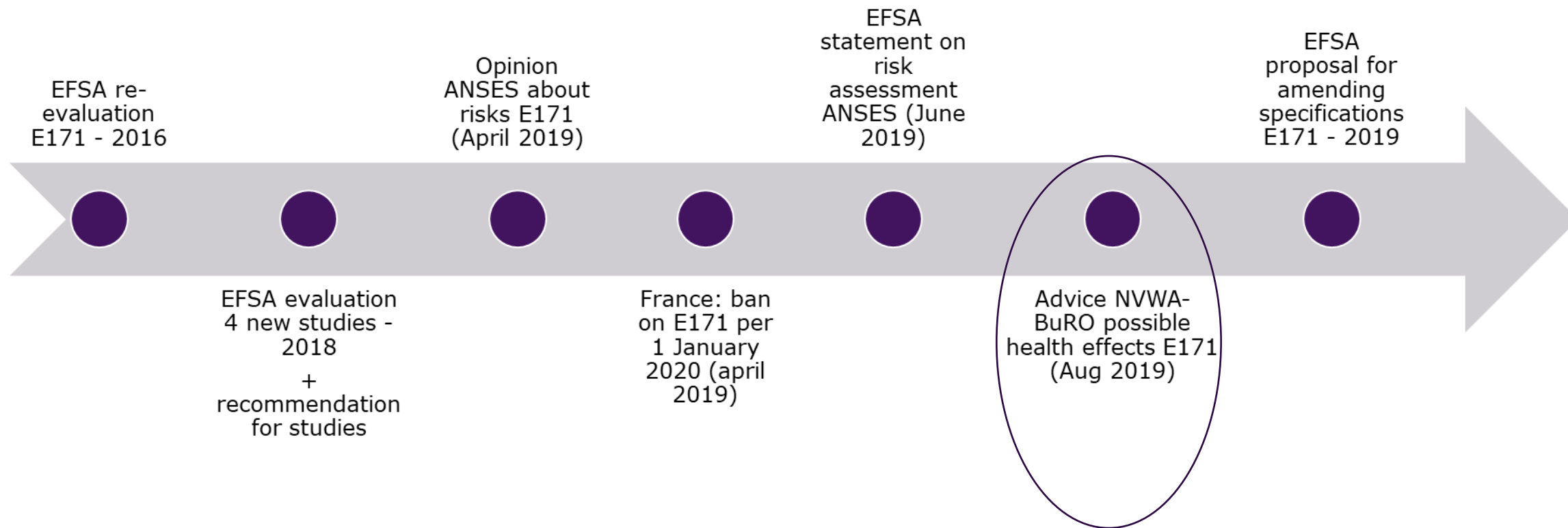
Ref.: BEUC-X-2019-031/MGO/cm

Brussels, 3rd May 2019

Subject: Civil society organisations demand the removal of E171 from the EU list of permitted food additives



Timeline risk assessments E171





BuRO: international workshop in July 2018

- › Conclusion from workshop participants: data recently published give rise to concern and further research is required to ascertain whether measures are required, and if so which measures
- › Other findings:
 1. Although E171 has been used in foods for about 50 years, the concentrations are unknown, as is whether its use is increasing
 2. E171 is widely used in confectionery, sauces and baked goods, and in toothpaste. It is merely used to improve the appearance of the food (colour, gloss) and has no nutritional value
 3. Children ingest relatively large amounts of E171 per kg body weight per day; however, the exact intake is unknown and estimates vary
 4. There are indications from laboratory animal and *in vitro* studies that adverse health effects may occur in consumers and in particular in people with increased intestinal permeability, after ingestion of E171. It is unknown whether there is a threshold value for these effects

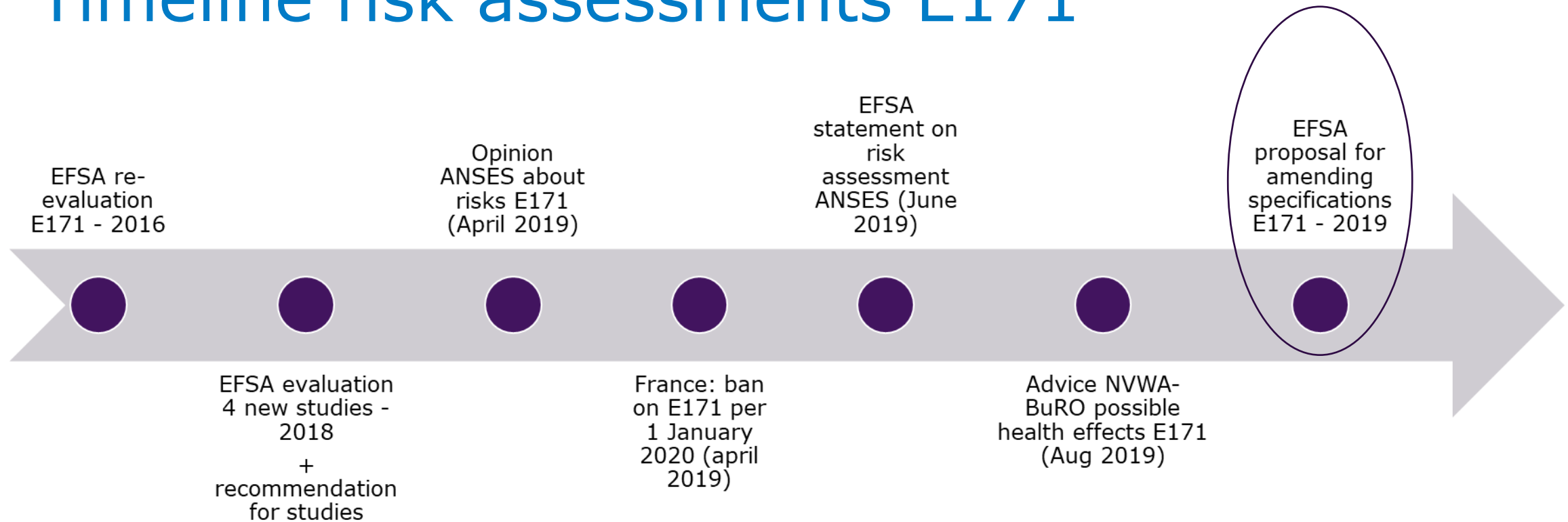


Opinion on possible health effects of the food additive titanium dioxide (E171), BuRO, 2019

- Studies conducted since 2016 in mice and rats provide an indication of tumour promotion by E171 in the intestinal tract, but should be considered 'exploratory' since they were not conducted in accordance with OECD guidelines
- With regard to the EOGRT study (ongoing at the time), an examination of immunotoxicological effects is important given recent studies, in addition to potential reprotoxicological effects
- Potential promotion of colon cancer by E171 should be examined; doubtful whether the performance of an EOGRT or chronic exposure test would be a suitable test system
- Further research in humans required to establish any relevance of experimental findings to man



Timeline risk assessments E171





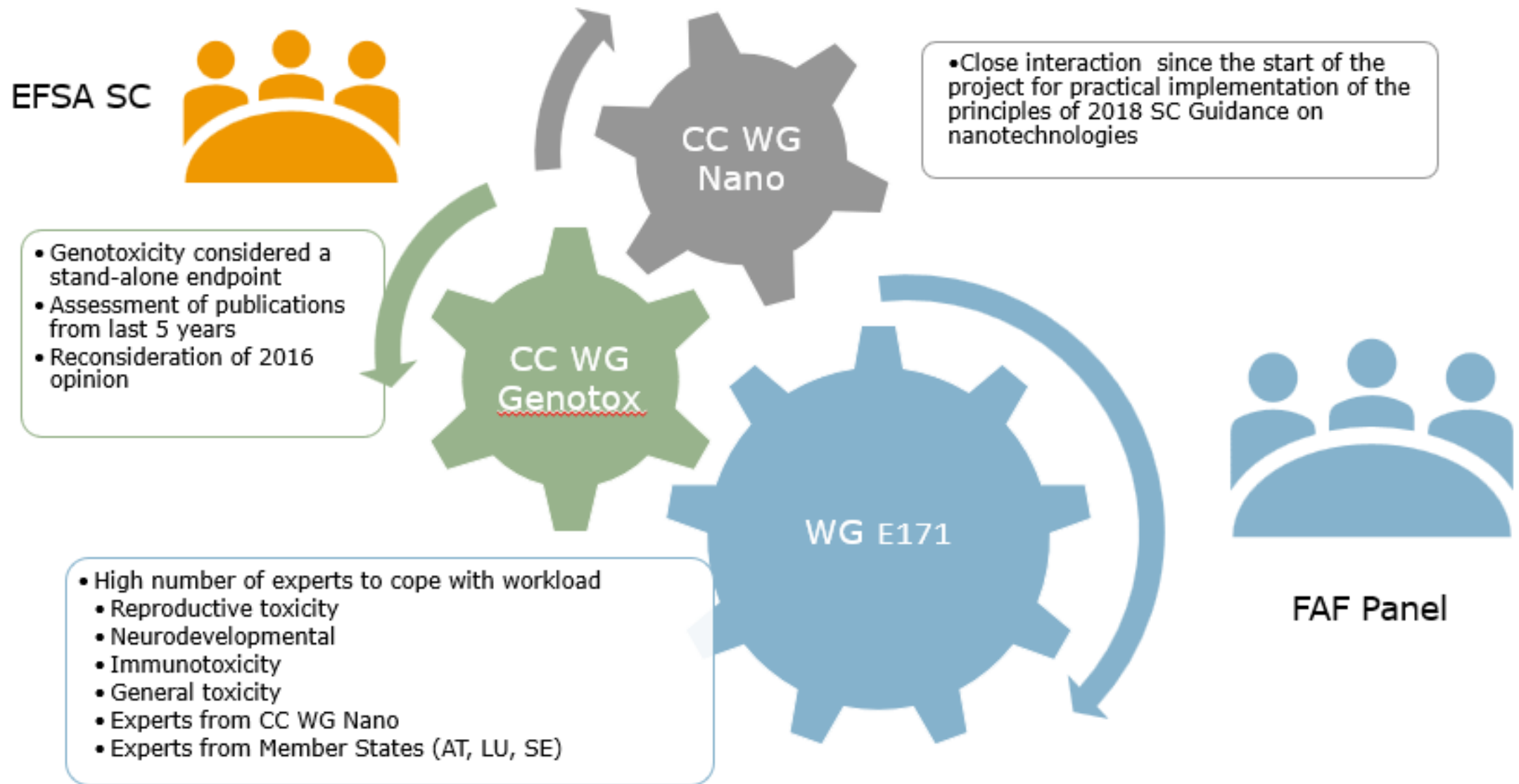
Updated opinion on safety assessment of titanium dioxide (E171) as a food additive, May 2021

- › Updated safety assessment of E171 based on new evidence
- › Including data obtained with TiO₂ nanoparticles (NPs)
- › And data from the extended one-generation reproductive toxicity (EOGRT) study
- › Literature search, January 2015–November 2020:
 - more than 11,000 publications retrieved
 - around 200 *in vivo* studies and 300 *in vitro* studies identified
- › In line with the data requirements specified in the 2018 EFSA SC Guidance on nano





Approach





Toxicokinetic studies

- › Focus on *in vivo* studies: ≈ 30 studies relevant for hazard characterisation and 33 studies for providing supporting evidence
- › Reliability assessed (1 to 4)
- › E171: low oral systemic availability (0.5%)
- › May pass the placenta and may be transferred to the fetus
- › Rat studies with TiO_2 NPs (7-90 nm) showed long half-lives (200–450 days), potential for accumulation, long time to reach steady state (3–5 years)
- › Oral systemic availability was low ($<1\%$). In tissues from deceased subjects, TiO_2 particles were identified in liver and spleen



EFSA risk assessment, conclusions on NP in E171

- › There is currently no limitation for the content of nanoparticles in E171
- › Data from business operators: <50% of constituent particles in E171 have minimum external dimension below 100 nm by number
- › Percentage by number of constituent particles <30 nm was $\leq 1\%$ in samples of pristine E171 or in E171 extracted from foods
- › TiO_2 particles in pristine E171 likely form large agglomerates. Following dispersion, these agglomerates may deagglomerate, resulting in increased 'free' nanoparticles, depending on conditions in food and GIT
- › The Panel concluded that studies with TiO_2 nanoparticles were relevant in the risk assessment of E171. However, studies performed with TiO_2 NPs that predominantly consisted of particles smaller than 30 nm were considered to be of limited relevance



Conclusions on absorption and toxicity of TiO₂ particles

- › Absorption of TiO₂ particles is low; they can accumulate in the body due to their long half-life
- › Studies on general and organ toxicity, including the new EOGRT study did not indicate adverse effects up to a dose of 1,000 mg/kg bw per day
- › Also, no effects were seen in studies retrieved from the literature with TiO₂ NP >30 nm up to the highest dose tested of 100 mg/kg bw per day
- › No effects on reproductive and developmental toxicity up to a dose of 1,000 mg/kg bw per day (highest dose tested) observed in the EOGRT study with E171
- › Immunotoxicity and inflammation with E171 as well as neurotoxicity with TiO₂ NPs may be indicative of adverse effects
- › There are indications of the induction of aberrant crypt foci with E171
- › No studies appropriately designed and conducted to investigate the potential carcinogenicity of TiO₂ nanoparticles



Conclusions on absorption and toxicity of TiO₂ particles, 2

- › TiO₂ particles have the potential to induce DNA strand breaks and chromosomal damage, but not gene mutations
- › No clear correlation was observed between the physico-chemical properties of TiO₂ particles (e.g. crystalline form, size of particles, shape and agglomeration state) and the outcome of either *in vitro* or *in vivo* genotoxicity assays
- › A concern for genotoxicity of TiO₂ particles in E171 could not be ruled out
- › Several modes of action for the genotoxicity may operate in parallel; relative contributions unknown and uncertainty about a threshold mode of action
- › Cut-off value for TiO₂ particle size with respect to genotoxicity not identified

→ Panel concluded that E171 can no longer be considered as safe when used as a food additive



Regulatory status E171, January 2022

- › October 2020, European Parliament called on the EC to withdraw its draft regulation, to apply the precautionary principle and to remove TiO_2 (E171) from the list of food additives authorised by the Union
- › Regulation (EU) 2022/63 to amend Regulation (EC) No 1333/2008 on food additives:
 - Given that EFSA had not identified an immediate health concern linked to E171 and in order to allow for a smooth transition:
 - Adding E171 allowed in manufacturing until 7 August 2022
 - Sales allowed until date of minimum durability or 'use by' date
 - Article 3: The Commission shall, following consultation on the European Medicines Agency, review the necessity to maintain titanium dioxide (E171) or to delete it from the Union list of food additives for the exclusive use as colour in medicinal products in Part B of Annex II to Regulation (EC) No 1333/2008 within three years after the date of entering into force of this Regulation



Uncertainties

- › Size distribution of the particles in marketed E171
- › Processes used by industry for E171 in food and to what extent these processes may affect the degree of agglomeration and thus internal exposure
- › State of agglomeration i.e. presence of 'free' particles (effect on absorption?)
- › Representativity of tested materials for the food additive E171 when used in food
- › Differences in physico-chemical properties of tested materials and impact on results
- › Reliability most widely used analytical technique, i.e. ICP-MS
- › Limited kinetic data
- › None of the rodent studies were sufficiently long to cover the time needed to reach steady state for accumulation
- › Relative contribution of molecular mechanisms leading to production of ROS resulting in the genotoxicity of TiO_2
- › Nature of the interactions between DNA and TiO_2 particles leading to conformational changes in DNA





Bischoff et al., Int J Molec Sci, 2020

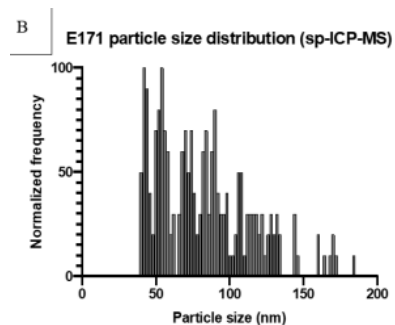
Review

Possible Adverse Effects of Food Additive E171 (Titanium Dioxide) Related to Particle Specific Human Toxicity, Including the Immune System

Nicolaj S. Bischoff ^{1,*}, Theo M. de Kok ¹, Dick T.H.M. Sijm ^{1,2}, Simone G. van Breda ^{1,3}, Jacco J. Briedé ^{1,4}, Jacqueline J.M. Castenmiller ², Antoon Opperhuizen ², Yolanda I. Chirino ^{3,5}, Hubert Dirven ⁴, David Gott ⁵, Eric Houdeau ⁶, Agnes G. Oomen ⁷, Morten Poulsen ⁸, Gerhard Rogler ⁹ and Henk van Loveren ²

Literature review (until Sept 2020) to address questions of BuRO on process of risk assessment of E171

Conclusions: the existing body of evidence raises concern for human health regarding the long-term ingestion of E171. The wide-spread human exposure in combination with the reported tumor-promoting and pro-inflammatory responses in animal experiments indicates the necessity to fill in the identified knowledge gaps that are crucial in the hazard identification and risk assessment process. A particular concern was identified for children due to their proportionally higher TiO_2 intake, and patients with IBD, given their potential risk of increased absorption, as a consequence of impaired intestinal health.



B) Size distribution of E171 particles (by single-particle ICP-MS) with a median particle size of 79 nm and 72% of particles < 100 nm

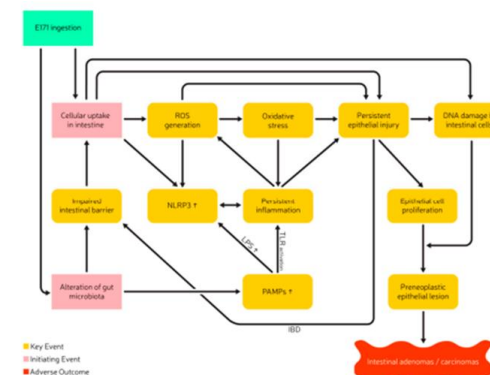


Figure 2. Postulated Adverse Outcome Pathway of TiO_2 after ingestion and related to inflammation and carcinogenicity, adapted and extended from Braakhuis et al. [3]. Abbreviation: ROS, reactive oxygen species; PAMPs, Pathogen-Associated-Molecular-Patterns; LPS, Lipopolysaccharides; IBD, Inflammatory Bowel Disease; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3, TLR, Toll-like receptor.

Mode of Action: many *in vivo* and *in vitro* studies showed that exposure to TiO_2 (NP) can result in the formation of ROS and the induction of genetic damage and that E171 has the potential to initiate and stimulate inflammation, promote tumors.



Peters et al. and Brand et al., Nanotoxicology 2020

- › Characterization and quantification of titanium (Ti) and TiO₂ in postmortem tissue samples from 15 deceased persons: liver, spleen, kidney and the intestinal tissues jejunum and ileum
- › Results total-Ti: ranging from <0.01 to 2.0 mg Ti/kg (median values of 0.02 (liver), 0.04 (spleen), 0.05 (kidney), 0.13 (jejunum), 0.26 (ileum) mg Ti/kg)
- › Particulate TiO₂ concentrations ranged from 0.01 to 1.8 mg Ti/kg (median values of 0.02 (liver), 0.02 (spleen), 0.03 (kidney), 0.08 (jejunum), 0.25 (ileum) mg Ti/kg)
- › Particulate TiO₂ explained 80% of the total-Ti concentration: most Ti is particulate material (primary particles, aggregates and agglomerates, 50–500 nm with a mode in the range of 100–160 nm. About 17% of the detected TiO₂ particles had a size <100 nm)
- › Brand et al. focused not only on the clinical and histopathological observations, but also used Adverse Outcome Pathways (AOPs) to consider earlier steps (Key Events)
- › Organ concentrations of Ti from oral animal studies were compared to concentrations found in human postmortem organs
- › TiO₂ can trigger a number of key events in liver and intestine. Ti levels in human intestinal tissue, spleen and kidney are similar or higher than those found in liver, suggesting these tissues may also be relevant

Acknowledgement:
Agnes Oomen

