PQRI Position Paper

Is there a Case for Banning Titanium Dioxide (E171) in Pharmaceuticals?

PQRI Workshop held in June 2023 in Washington DC, explores the feasibility of replacement of titanium dioxide from a technical and regulatory point of view. World-class experts examine the safety of titanium dioxide, its potential replacements and what its ban would mean for the availability of medicines in Europe which are predicted to be severely affected should such a ban come into force.

1/22/2024

This position paper was compiled from key information shared by many world-class experts at a PQRI TiO_2 Workshop which took place in Washington DC in June 2023 to discuss the science related to TiO_2 safety and reformulation challenges with using TiO_2 alternatives currently on the market. The position paper was prepared by the TiO2 Workshop Organizing Committee and workshop presenters.

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Executive Summary

In June 2023 the Product Quality Research Institute (PQRI) held a 2-day workshop to discuss why titanium dioxide (TiO_2) should not be banned for use in pharmaceuticals.

For decades TiO_2 has been used widely in cosmetics, medicines and foods due to its safety and utility. Food-grade TiO_2 (known as E171) was recently banned for use in foods and dietary supplements in the European Union (EU), and, according to EU law, there is a potential that TiO_2 could also be banned there as well in pharmaceuticals as early as 2025. As an estimated 91,000 drug products in the EU contain titanium dioxide, and a ban on its use could have a significant impact of the availability of drugs for patients in Europe, but as a consequence, possibly worldwide.

Titanium dioxide has unique performance qualities, beyond being a colorant, required in solid oral dosages including opacity (protection from UV light) and the ability to protect printing elements on tablets and capsules. No other excipient that might serve as a replacement could perform an equivalent function in either the capsule shell or the tablet coating. In addition, even if a direct replacement were found, reformulation of ***each*** drug product is estimated to take 30-60 months and require a large investment of resources, possibly also involving new stability and bioavailability studies. Similarly large resources would be required in the registration, approval and launch of each reformulated drug product. This would result in many drugs becoming unavailable in the EU and exacerbating current drug shortages.

Most importantly, there isn't a safety reason to trigger this change. Despite the fact that there were no studies showing direct interaction of E171 with DNA, the European Food Safety Authority (EFSA) concluded in 2021 that a genotoxicity concern could not be ruled out and that E171 could no longer be considered safe in food. However, in assessing the potential health effects of E171, EFSA based its evaluation on studies in which laboratory animals were exposed in ways that are not reflective of human food exposures, such as sonication in water. They also appear not to have rigorously evaluated the biological relevance of the test systems, the robustness of the study designs or the reliability of the data. Rather than do a formal risk assessment, EFSA did a hazard evaluation that focused on TiO_2 nanoparticles which were not representative of E171 or relevant for assessing E171 as a food additive.

In light of EFSA's concerns for genotoxicity, an independent panel of experts conducted a rigorous weight of evidence review of the genotoxicity of all grades and sizes of TiO_2 (published in Kirkland et al., 2022). The panel approach was different from that of EFSA, excluding certain studies that are only indicator tests, and evaluating the robustness of the study designs and the reliability of the data. The panel concluded that the existing evidence from reliable, relevant and robust tests does not support a direct DNA damaging mechanism for TiO_2 (nano and other forms). However, more confident conclusions could be reached if there were more robust data on relevant endpoints (e.g. *in vivo* gene mutations) and mode of action, and such studies are planned.

In addition, after the PQRI conference, Japan's Ministry of Health, Labour and Welfare (MHLW, 2023) published a study that specifically addressed the potential concern for genotoxicity with TiO_2 nanoparticles. Studies in rats using 6 nm TiO_2 nanoparticles at doses up to 1,000 mg/kg/day, i.e., equivalent to 50 grams/day for a person found no preneoplastic changes or evidence of genotoxicity. In addition, there are no consistent, reliable studies showing an effect on the immune system. Furthermore, many regulatory agencies have now concluded the safety of TiO_2. Food Safety Australia/New Zealand (2022), Health Canada (2022), JECFA (2023) and US FDA (2023) have all

concluded TiO_2 does not present a genotoxic hazard in vivo. These conclusions are crucial since the exposure of concern for people is in vivo. Considering these conclusions and that a form of TiO_2 equivalent to E171 tested negative in an oral carcinogenicity study (NCI, 1979) at the maximum dose possible, i.e., 5% of the diet, which is equivalent to 2,250 mg/kg/day or 112.5 grams/day for a 50 kg person, no genotoxic risk to people would be expected whether TiO_2 is ingested from food, or from medicines where the exposures are orders of magnitude lower than in food.

The suppliers of film coating systems and capsule shells have shown that finding a replacement to E171 which has similar opacity, whitening power and regulatory acceptability will be difficult. In addition, there are other unique and unmatched attributes that titanium dioxide affords which the alternatives do not have, e.g., inert nature, high melting point, negligible solubility across the pharmaceutical pH range and ability to undergo a specific and reproducible color change in response to laser irradiation. The suppliers' observations have been confirmed by the pharmaceutical industry as they have evaluated the currently available E171 alternative film coating systems and capsule shells. In the end there is no workable replacement for E171 that meets the functional needs of the pharmaceutical industry and the toxicological concerns of the regulators.

In summary, there really is no significant safety risk to the use of TiO_2 (such as E171) in pharmaceuticals and therefore no case for a ban. However, there will absolutely be significant unintended, but predictable consequences to public health if TiO_2 were to be banned for use in these applications due to the associated drug shortages which would occur. There is a significant benefit to the continued use of TiO_2 in pharmaceuticals that has been demonstrated in the information contained in this paper and that must be weighed appropriately in deciding whether to extend the ban of E171 to pharmaceuticals.

Introduction and Background (presented by D. Schoneker – PQRI Workshop Chair)

Titanium dioxide (also known as E171 or TiO_2) has a long history of safe use across many global industries with several applications in cosmetics, medicines, and food. E171 has recently been banned for use in foods and dietary supplements in Europe, and there is a potential that E171 could also be banned in pharmaceuticals in the European Union (EU) as early as 2025. The EU is currently evaluating an extension of the E171 ban to pharmaceuticals, and the impact of the potential ban would have serious consequences for the availability of many drugs for European patients.

The European Food Safety Authority (EFSA) re-evaluated the safety of E171, and although there were no studies showing direct interaction of E171 with DNA, EFSA concluded in May 2021 that a genotoxicity concern could not be ruled out and that E171 can no longer be considered safe in food. A ban on its use in foods was then quickly proposed by the European Commission (EC).

The Product Quality Research Institute (PQRI) held a workshop on June 13-14, 2023, to discuss the science related to the use of Titanium Dioxide (TiO_2) in pharmaceutical applications. TiO_2 is an extremely important colorant and excipient in thousands of drug products all over the world that patients have been safely using for decades with no indication of any safety concerns.

PQRI wanted to explore the scientific facts related to the safe use of TiO_2 in pharmaceuticals and help develop a good understanding of the actual safety profile of TiO_2 and assess the challenges that industry has seen in trying to find suitable alternatives to TiO_2 for pharmaceutical applications.

An objective of the workshop was to bring together material suppliers, the pharmaceutical industry, and regulatory experts to discuss the impact that removing titanium dioxide would have along with the benefits and challenges of the alternatives to titanium dioxide for use in solid oral dosage forms. The workshop addressed the following key areas:

- Built awareness for the industry by giving an overview of the issue, an evaluation of the data related to TiO_2 safety, and the potential impact a ban out titanium dioxide would have on patients.
- An overview of global consequences due to the EU TiO_2 regulation.
- Present the technical challenges that pharmaceutical companies are likely facing when trying to formulate new and reformulate existing drug products with the currently available alternatives.
- Identify areas that need further research to support technical initiatives related to possible additional safety study requirements to support continued safe use of TiO_2 or technologies related to the use of TiO_2 alternatives where desired.

This paper contains key information from the PQRI Workshop that needs to be considered by Health Authorities, in particular EMA before developing their recommendation to the EU Commission about whether to extend the TiO_2 ban to pharmaceuticals. The sections below provide an overview of the significant information that was presented by the expert speakers who participated in the workshop as well as ideas that were discussed during Breakout Sessions that were held to get broad feedback from the participants on several key points related to TiO_2 safety and the challenges of using TiO_2 alternatives in many drug applications.

References

- Commission Regulation (EU) 2022/63 of 14 January 2022 amending Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council as regards the food additive titanium dioxide (E 171) (Text with EEA relevance), https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv%3AOJ.L_.2022.011.01.0001.01.ENG

Critical Considerations About the Basis for EFSA's Opinion on TiO_2 Safety in Foods – (presented by D. Lockley)

Contrary to its opinions in 2016 and 2018, the European Food Safety Authority (EFSA) Scientific Panel concluded that a concern for genotoxicity could not be excluded in its 2021 opinion on the titanium dioxide (TiO_2) food additive, E171 (EFSA, 2021a).

EFSA concluded nanoparticles could accumulate in internal organs over time based on genotoxicity tests (and other studies) conducted with non-food grade TiO_2 nanomaterials to cause genotoxicity via suggested but unproven mechanisms:

- During cell division, reactive oxygen species (ROS) and enzymes generated from macrophages, are produced within the cytoplasm or in the nuclear space to induce chronic inflammatory responses which can damage nearby normal tissue.
- Direct, non-covalent binding to chromosomal and/or mitochondrial DNA, causing conformational changes and influencing DNA replication during cell division.
- Binding to centromeres or other structures involved in cellular division and proliferation, hence interfering with proper chromosomal segregation during cell division.

However, through the inconsistent use of its new nano guidelines (2021b), EFSA rated research in a very selective manner, ignoring in its weight-of-evidence assessment a number of relevant studies that show a high degree of particle agglomeration / aggregation within the gastrointestinal tract (Figure 1, taken from Marucco et al., 2020), negligible oral bioavailability, and a lack of potential genotoxicity of grades of TiO_2 that are representative of E171 as used in foods (Kirkland et al., 2022).

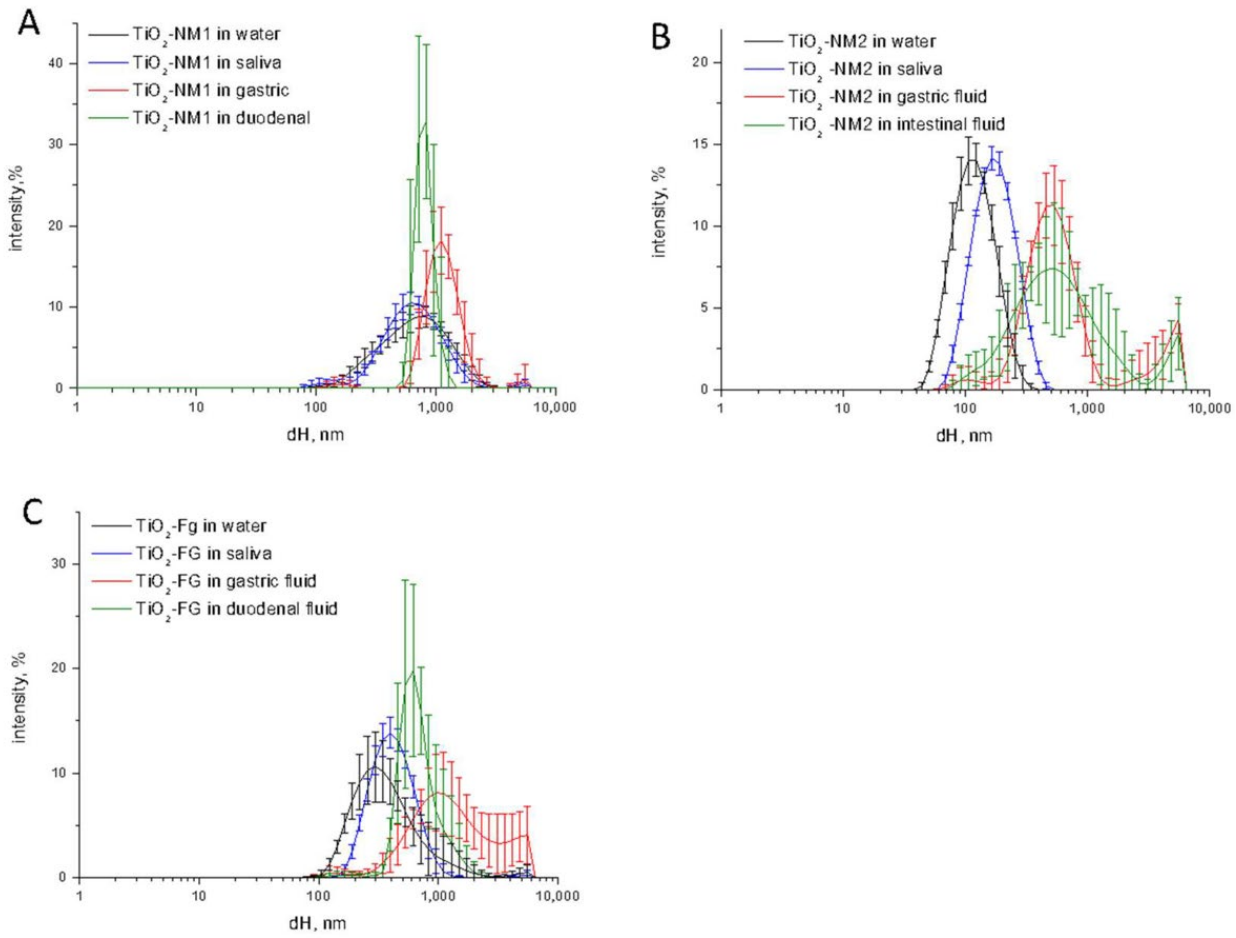

Figure 1: Size distribution monitored by DLS of the TiO_2 samples during the digestion cascade. (A) TiO_2-NM1; (B) TiO_2-NM2 (C) TiO_2-FG. Hydrodynamic diameters (d_H) distribution (% intensity) is expressed as mean value of 5 measurements in three independent experiments ± SD (taken from Marucco et al., 2020)

EFSA (2021a) stated that the results of genotoxicity testing on TiO_2 nanoparticles with constituent particle number-average sizes smaller than 30nm should not be considered. However, for completeness, EFSA then published the findings of multiple in vitro and in vivo genotoxicity tests on such test materials, as well as the results of genotoxicity testing on other test materials with number-average particle sizes greater than 30nm. Unlike E171, these nanomaterials include significant particle fractions and resulted in:

- Some of the nanomaterials testing positive in micronucleus (MN) and Comet assays, leading EFSA to conclude that by analogy the safety of E171 is questionable.
- Long elimination half-lives for TiO_2 particles in major internal organs were estimated following parenteral or, in certain cases, oral gavage exposure to these test materials.
- EFSA (2021a) suggesting that available data are insufficient to identify TiO_2 particle doses / concentrations below which genotoxicity will not occur in tissues containing these particles.

Interestingly, EFSA (2021a) highlights several issues that should be examined while evaluating its conclusions, including:

- EFSA based its evaluation of the genotoxicity endpoint primarily on genotoxicity assays of test materials that are not typical of the food additive E171 utilising techniques of exposing test animals that are not indicative of human food exposures such as sonication in water.

- In comparison to E171, EFSA (2021a) did not evaluate changes in manufacturing techniques or variances in the composition and other features of test nanomaterials.

- Based on the results of experiments that do not represent E171 or are relevant for assessing E171 as a food additive, EFSA (2021a) essentially did a hazard evaluation of TiO_2 nanoparticles that are not representative of E171 or relevant for assessing E171 as a food additive.

Following the mandate of the EU commission and discussions with EFSA, studies submitted to EFSA as part of the Titanium Dioxide Manufacturers Association (TDMA) comprehensive science plan to support the safety of TiO_2 were created over a number of years to update the database using the latest OECD standards and methodology. However, in light of the EFSA (2021a) Opinion, TDMA set up an independent panel of experts to carry out a robust, scientific review of all toxicological aspects of TiO_2. This panel focused on understanding the genotoxicity hazard and produced an expert review (Kirkland et al., 2022) which recommended further testing and studies update the TDMA scientific programme.

References

- EFSA (2021a). Safety assessment of titanium dioxide (E171) as a food additive. EFSA Journal 19(5):, 6585
- EFSA (2021b). Guidance on risk assessment of nanomaterials to be applied in the food and feed chain: human and animal health. EFSA Journal 19(8): 6768
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- Marucco A, Prono M, Beal D, Alasonati E, Fisicaro P, Bergamaschi E, Carriere M, Fenoglio I (2020). Biotransformation of Food-Grade and Nanometric TiO_2 in the Oral–Gastro–Intestinal Tract: Driving Forces and Effect on the Toxicity toward Intestinal Epithelial Cells. Nanomaterials, 10(11), 2132.

Critical reviews of TiO_2 safety relevant to the EFSA Opinion

- ***Genotoxicity (presented by D. Kirkland)***

Titanium dioxide was considered no longer safe for use in foods (nano and microparticles of E171) by the European Food Safety Authority (EFSA) who concluded that "a concern for genotoxicity could not be ruled out". An independent panel of experts, not currently employed by companies that manufacture and sell TiO_2, developed a weight of evidence (WoE) assessment of the genotoxicity of all types of TiO_2 based on the available data, and this was published in Kirkland et al. (2022).

A total of 192 datasets for endpoints and test systems considered the most relevant for identifying mutagenic and carcinogenic potential were reviewed and discussed for both reliability and relevance (by weight of evidence) and in the context of whether the physicochemical properties of the particles had been characterized, both as supplied materials and in the preparations (culture media, dosing formulations) used for the studies. Of the 192 datasets identified, only 34 met the reliability and quality criteria for being most relevant in the evaluation of genotoxicity. It should be noted that of these 34, only 3 datasets (all *in vivo*) used E171, or Unitane 220 which is considered comparable to E171. Of these 34 datasets, 10 were positive (i.e. reported evidence that TiO_2 was genotoxic), all of which were from studies of DNA strand breakage (comet assay *in vivo*) or chromosome damage (micronucleus or chromosome aberration assays) *in vitro* or *in vivo*. All the positive findings were associated with high cytotoxicity, oxidative stress, inflammation, apoptosis, necrosis, or combinations of these, and, considering that DNA and chromosome breakage can be secondary to physiological stress, it is highly likely that the observed genotoxic effects of TiO_2, including those with nanoparticles, are secondary to physiological stress. Consistent with this finding, there were no positive results from the *in vitro* and *in vivo* gene mutation studies evaluated although it should be noted that to definitively conclude a lack of mutagenicity more robust *in vivo* gene mutation studies would be useful.

The approach of the expert panel was different to that of EFSA, as can be seen from Table 1, and so it is not surprising that different conclusions were reached. In summary the main differences were:

1. EFSA included a large number of *in vitro* comet assays, of which nearly 72% were positive, whereas the expert panel excluded these since they are only indicator tests (DNA strand breaks may be repaired or lethal and may not be converted to stable genetic changes such as mutations).
2. EFSA accepted the conclusions of the authors of published papers without further review whereas the expert panel undertook a detailed examination of the 192 datasets in order to establish the acceptability of the study design, quality, reliability and interpretation of the data, and conclusions of the published papers.

Table 1: Comparison of EFSA and Expert Panel studies considered appropriate for review and included in the final assessments.

	EFSA approach		Expert Panel approach	
Study type	**No. of studies available for evaluation**	**No. of studies achieving High or Limited relevance (No. positive)**	**No. of datasets reviewed**	**No. achieving Moderate or higher weight after WoE assessment (No. positive)**
In vitro				
Bacterial reverse mutation (Ames test)	8	0	15	0
Mammalian cell gene mutation	14	7 (3 positive)	16	2 (0 positive)
MN or CA	56	43 containing 67 datasets (26 datasets positive)	62	12 (2 positive)
Comet assay	142	106 containing 142 datasets (102 datasets positive)	0	0
DNA binding	5	5 (unclear whether these considered positive)	0	0
8-OHdG adducts	5	5 (4 positive)	0	0
γH2AX foci	4	4 (2 positive)	0	0
ToxTracker	1	1 (0 positive)	0	0
Sub-totals	**235**	**231 datasets (137 positive)**	**93**	**14 (2 positive)**
In vivo				
Gene mutation	6	6 (1 positive)	9	2 (0 positive)
MN or CA	26	15 (8 positive)	35	13 (7 positive)
Comet	44	18 containing 19 datasets (12 datasets positive)	51	3 (1 positive)
DNA binding	2	2 (unclear whether these considered positive)	0	0
8-OHdG adducts	2	1 (1 positive)	4	2 (0 positive)
γH2AX foci	2	2 (2 positive)	0	0
Sub-totals	**82**	**45 (24 positive)**	**99**	**20 (8 positive)**
Totals	**317**	**276 (161 positive)**	**192**	**34 (10 positive)**

Note: Studies measuring formation of reactive oxygen species, epigenetic DNA methylation and cell transformation were discussed in the EFSA opinion, but not included in the table above since they appear to be taken as supporting information rather than direct evidence of genotoxic effects.

The authors therefore concluded that the existing evidence does not support a direct DNA damaging mechanism for titanium dioxide (nano and other forms).

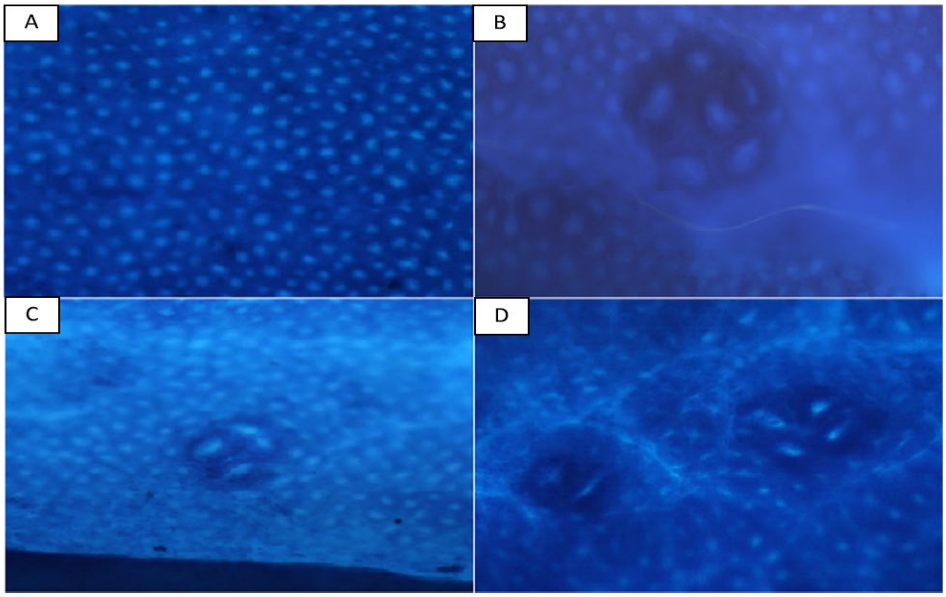
- ***Carcinogenicity (presented by S. Cohen)***

The carcinogenicity of TiO_2 (Unitane 0-220, in the anatase form) was evaluated in a full two-year bioassay in both rats and mice performed by the National Toxicology Program (NTP, 1979). Recent investigations have demonstrated that this material is very similar to E171. It was administered in the diet at levels of 2.5 and 5% (25,000 and 50,000 ppm) in addition to a control group at 0%. The 5% dose is more than 100 times higher than that used in the Bettini et al. (2018) short-term study described below, and is the maximum level allowed for chronic toxicity studies to avoid nutritional abnormalities. A short-term 14-day study where TiO_2 was administered up to 10% of the diet showed no adverse effects.

NTP concluded that there was no effect on survival or weight gain, and there were no incidences of any tumors above historical or concurrent controls. In addition, there was no evidence of increased non-neoplastic effects above background, and specifically there was no evidence of increased incidences of pre-neoplastic changes such as hyperplasia. This included a complete lack of any effect on the gastrointestinal (GI) tract, including the colon.

Shorter term studies, approximately 110 days or less, have also been performed in rats and mice, evaluating the effects of TiO_2 primarily on the GI tract, especially the colon, as well as an assessment of possible immune effects. A surrogate marker for predicting colon carcinogenesis is aberrant crypt foci (ACF) in the colon (Fig. 2), but the evidence for an association between ACF and colon cancer is contradictory. Importantly, the large foci and dysplastic foci are not well defined, and there is no good historical control database for the studies that were reported with E171, particularly when using pretreatment with genotoxic carcinogens as the baseline.

Fig.2: Aberrant crypt foci (from Shwter et al., 2016)



In the Bettini et al. (2017) report, there was a claim of an increase in ACF following E171 administration as well as an effect on various immune markers, but there are reasons to question the validity of this study.

The doses used in this experiment were 0.2 and 10 mg/kg body weight, administered in the drinking water for either 7 or 100 days, respectively. The difficulty of administration in the drinking water is that TiO_2 is insoluble. To help disperse the material, the TiO_2 suspension was sonicated. However, this method is not an appropriate form of administration for evaluating dietary exposure. In addition, E171 was only administered after dimethylhydrazine (DMH) pre-treatment. DMH is a potent genotoxic colon carcinogen and gives highly variable numbers of ACF in shorter-term experiments, and there are no established historical ranges for ACF induced by DMH. Ultimately, most of the animals treated with DMH develop tumors in longer-term assays. In the Bettini et al. (2017) experiment, there were no groups administered E171 without pre-treatment with DMH, making an evaluation of effects of E171 essentially impossible. Furthermore, there were several methodological issues with this experiment, including lack of standardization of tissue sample selection, but most importantly, the results were not evaluated in a blinded fashion.

In the publication by Urrutia-Ortega et al. (2016), a different model was used. This is the so-called colitis-associated colon cancer model in mice, which involves administration of the E171 after pre-treatment with both azoxymethane (AOM) by intraperitoneal administration, plus treatment with 2% dextran sulfate sodium (DSS) in water to produce colitis. AOM is the metabolite of DMH that is a more proximate form of the carcinogen that produces colon cancer. This model shows extreme variability of response in the colon, primarily because of the combination of both a genotoxic stimulus (AOM) and inflammation produced by 2% DSS. E171 was administered by gavage in water at a level of 5 mg/kg for eleven weeks in the study. There were only 6 mice per group, which is inadequate for proper statistical evaluation, and the results were not evaluated in a blinded fashion. They also used an assessment of goblet cells as an indicator of an effect on the intestine, but there was no standardized sampling and there was no control for tangential sectioning, which could markedly affect the results. They claimed that there were no tumors with control or with E171 alone, an important result to note for E171. There were 7 tumors with AOM plus colitis treatment and 21 tumors with AOM plus colitis plus E171, with an apparent decreased number of goblet cells with the latter treatment combination. However, the tumors were assessed only by gross observation of measurement and number. No histologic evaluation was performed, and it is highly likely that none of the lesions that were called tumors were actually epithelial neoplasms but rather represented inflammatory changes and/or lymphoid aggregates. The tumor numbers cannot be evaluated statistically, and there is no information regarding historical controls from this laboratory on the number of lesions that are expected in the colitis-AOM model itself.

In an attempt to address many of the deficiencies of the Bettini et al. (2017) and Urrutia-Ortega et al. (2016) studies, Blevins et al. (2019) performed a similar experiment that used dietary administration of E171 to larger groups rats (15/group), and included more dose levels (0, 40, 400, and 5,000 ppm, which was measured as approximately 1, 3, 20, and 250 mg/kg body weight). Some of these doses were comparable to those in the Bettini et al. (2017) study, but a dose approximately 10 times higher was included. In addition, there were groups treated with E171 both with and without DMH pre-treatment. Tissue sampling was standardized, and all evaluations were performed in a blinded fashion. There was essentially no effect on immune parameters (see next section), and there was no evidence of an increased incidence of ACF at any dose (see Table 2). In the DMH group (without TiO_2), there was one rat with two invasive adenocarcinomas, one rat in each of the DMH plus 40 ppm E171 and DMH plus 400 ppm E171 groups had an adenoma. Special care was taken to avoid tangential sectioning and standardization of

sampling for evaluation of the goblet cells. Utilizing these methods, there was no evidence of a difference in goblet cells between groups.

Table 2: Results from Blevins et al. (2019)

Group	Treatment	Total cm2 Evaluated	Mean No. of ACF/cm2,[a]	Mean No. of ABC/cm2,[a]
1	0 ppm E 171	25.4	0.8 ± 0.5	1.9 ± 1.1
2	40 ppm E 171	19.7	0.1 ± 0.1	0.2 ± 0.2
3	400 ppm E 171	27.6	0.9 ± 0.4	2.1 ± 1.1
4	5000 ppm E 171	23.9	0.9 ± 0.5	2.7 ± 1.6
5	180 mg/kg DMH · 2HCl	24.2	5.4 ± 1.2[b]	17.1 ± 4.1[b]
6	180 mg/kg DMH · 2HCl + 40 ppm E 171	27.3	5.3 ± 1.3[c]	14.8 ± 3.9[c]
7	180 mg/kg DMH · 2HCl + 400 ppm E 171	30.4	7.2 ± 1.3[d]	19.7 ± 3.6[d]
8	180 mg/kg DMH · 2HCl + 5000 ppm E 171	26.9	10.1 ± 2.6[e]	28.4 ± 6.6[e]

a Results expressed as mean ± S.E. N = 15 for groups 1 and 6–8 and 14 for groups 2-5.
b Significantly different compared to 0 ppm E 171 group, $p < 0.05$.
c Significantly different compared to 40 ppm E 171 group, $p < 0.05$.
d Significantly different compared to 400 ppm E 171 group, $p < 0.05$.
e Significantly different compared to 5000 ppm E 171 group, $p < 0.05$

More recently, Bischoff et al. (2022) utilized administration of E171 in drinking water or by gavage (in water) in a transgenic mouse intestinal cancer model. The National Cancer Institute strongly recommends not using this model for carcinogenesis evaluation as there is a very high background incidence of tumors with marked variability from animal to animal in number and size of tumors; such variability was actually seen in the Bischoff et al. (2022) study. Most importantly, there were no statistically significant findings in this study. Kaminski and Cohen (2023) have published a letter to the editor detailing many of the deficiencies of this particular study, but most notably, there were no statistically significant findings in the study, negating the extensive conjecture in interpretation by the authors.

An extended one generation reproductive (EOGRT) study was performed under GLP conditions and according to OECD 443 guideline. E171 was administered in the diet at doses of 0, 100, 300, and 1,000 mg/kg body weight/day for 122 days utilizing groups of 10 males and 10 females per group. ACF were evaluated in the F0 generation of the rats. There were no groups pretreated with DMH or AOM plus DDS. There were no ACF formed in any of the rats, although 7 rats had minimally increased variability in crypt sizes, and these were distributed across all of the groups. Thus, there is strong evidence when E171 is

administered in the diet that there is no effect on purported pre-neoplastic lesions (ACF) and no evidence of an effect on immune markers or on histology of other tissues that were examined. In this EOGRT study, there were no adverse effects, including reproductive parameters.

One of the concerns raised by EFSA refers to the nano subset of TiO_2 present in E171 that may have a potential for carcinogenic and immune effects. However, this was addressed specifically in the recent publication by Akagi et al. (2023) in which TiO_2 nanoparticles with the crystallite diameter of 6 nm were administered by gavage to rats for 28 or 90 days. The doses used in the 28-day study were 0, 10, 100, and 1,000 mg/kg bw/ day and in the 90-day study the doses were 0, 100, 300, and 1,000 mg/kg bw/day. They observed no treatment-related adverse effects on survival, body weight, hematology, urinalysis, serum chemistries, or organ weights. They observed TiO_2 particles present in the GI lumen and in the nasal cavity epithelium and stroma as well as in intestinal Peyer's patches, cervical and mediastinal lymph nodes and bronchus-associated lymphoid tissue. However, there was no evidence of inflammation around the particles, and most importantly, in an examination of the colon, there was no increase in proliferation, no increase of β-catenin expression nor a change in nuclear/cytoplasmic translocation (markers of dysplasia). In addition, *in vivo* genotoxicity assessments for micronuclei or γ-H2AX foci in hepatocytes were negative. Thus, even specifically evaluating the nano sized TiO_2, there was no effect on the colon including no evidence of inflammation or pre-neoplastic changes or evidence of genotoxicity.

Human carcinogenesis is due to either DNA reactivity (genotoxicity), immunomodulation, estrogenic activity, or cytotoxicity and regenerative proliferation. As is detailed by Kirkland et al. (2022), there is no evidence of direct genotoxicity with TiO_2 *in vivo*. Furthermore, there is no evidence of immunosuppression or estrogenic activity in any of the animal studies that have been performed including the 2-year bioassay, and there is no evidence of cytotoxicity and regeneration. Thus, TiO_2 has none of the properties that are attributed to known human carcinogens.

In summary, the NTP 2-year bioassay was completely negative involving administration of E171-like material to rats and mice at doses up to 5% of the diet. There was no evidence of an increase in tumors, and no adverse effects whatsoever including pre-neoplastic changes. The short-term assays provide no credible evidence for an effect on colon toxicity or proliferation, and no effect on immune markers. Based on all this data, it can be confidently concluded that TiO_2 is not carcinogenic when administered orally.

- ***Immunologic and Intestinal Effects of Dietary E 171 (Food Grade Titanium Dioxide) Consumption (presented by L. Blevins)***

In recent years, the safety of dietary E171 consumption has been called into question despite over 50 years of its use as a food additive. This has been due, in part, to an increase in studies suggesting that E171 dysregulates immune responses in the gastrointestinal (GI) tract and promotes neoplastic lesions. These studies often supplied E171 either through oral gavage or in drinking water despite E171 being water insoluble. This route of E171 exposure is not relevant to human E171 exposure. Furthermore, incorporation of E171 into food preparations creates a corona of food material around the E171 particles and changes how the GI tract interacts with the particles themselves. Specifically, the study by Bettini et al. (2017), which was instrumental in influencing the decision to ban E171 from European food stuffs, also did not evaluate the effects of E171 alone, only in combination with a known intestinal genotoxic carcinogen, dimethylhydrazine (DMH).

To address the aforementioned experimental pitfalls, the objectives of our study were to evaluate the acute (7 days) and long term (100 days) effects of dietary E171 exposure on the immune system of the gastrointestinal (GI) tract and periphery as well as to evaluate chronic exposure either alone or after pre-administration of DMH (Blevins et al., 2019). E171 was incorporated into 'chow' in increasing parts per million (ppm) content and fed to rats for 7 or 100 days. Following the 7- and 100-day feeding periods, rats were euthanized and measurements of inflammatory cytokines and phenotyping of immune cells in the periphery and GI tract were performed. Peyer's patches, peripheral blood mononuclear cells (PBMC), and spleen cells were analyzed for inflammatory and regulatory T-cell responses directly ex vivo or after in vitro stimulation (7 days). All tissues were collected from well-defined areas, and measurements, procedures, and evaluations were performed in a standardized and blinded manner.

When tissue specific and peripheral immune cells were assayed for phenotypic markers, we found that there were no statistically significant changes in the frequencies of any of the immune cells assayed due to dietary E171 alone or in combination with DMH. This included immune cell populations identified as being diminished by E171 administration by previously published reports such as T-regulatory cells and activated T-helper cells (Figs3 and 4). Further, when the profile of inflammatory cytokines present in the GI and blood were determined, we observed no significant change in any of the immune cytokines tested as a result of E171 administration. Notably, there were 2 instances of statistically significant changes in inflammatory cytokines; IL-12 was significantly elevated in the plasma of rats pretreated with DMH and fed chow with 40ppm of E171, and IL-17 was significantly elevated in the colon of rats pretreated with DMH and fed chow with 400ppm of E171. In both instances these statistically significant changes were present only in animals that had received both DMH and E171 and neither demonstrated any dose-response relationship as the effect was lost in the higher E171 containing groups in both cases calling into question the biological significance of these changes.

Fig. 3: Activated T-helper cells

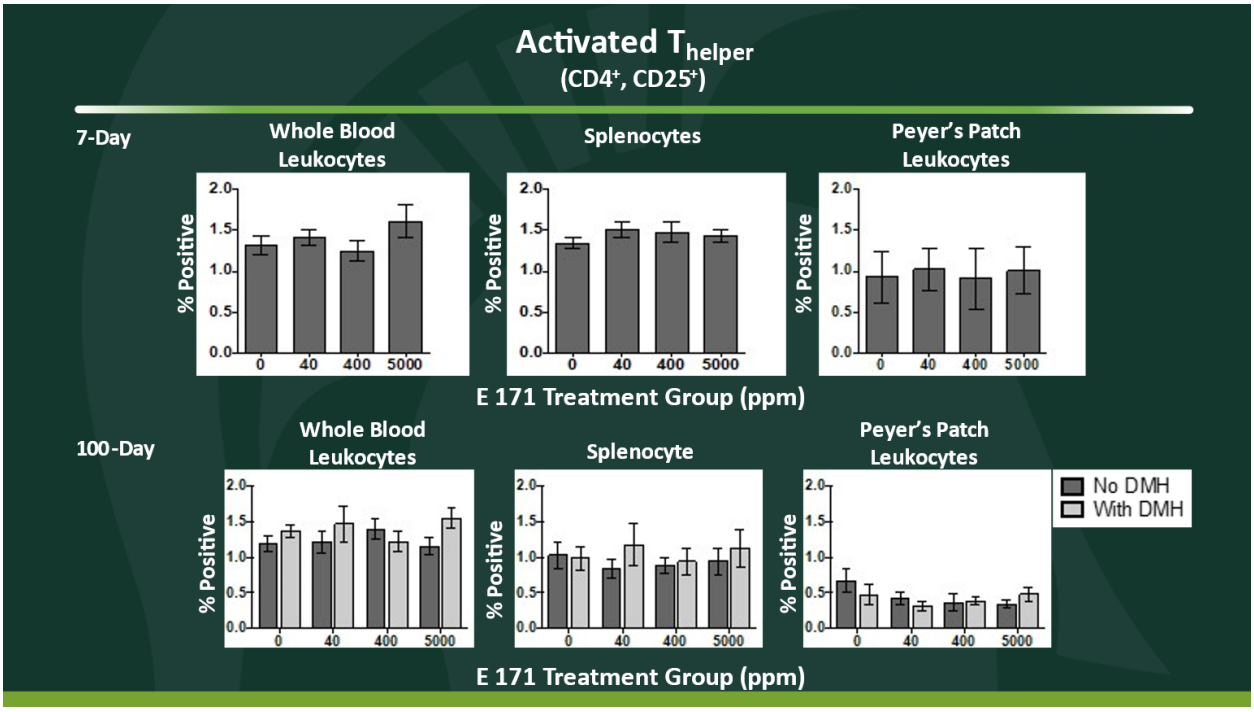
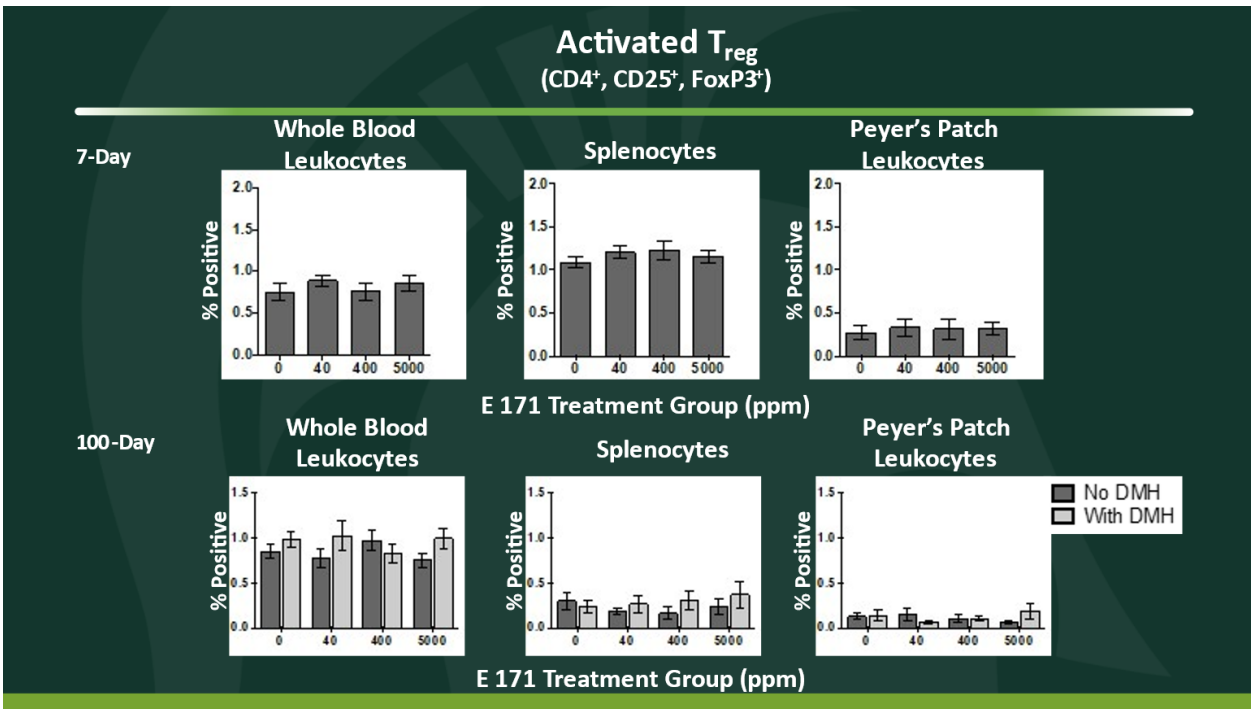


Fig. 4: Activated T-regulatory cells



Despite the stark contrast of our results to Bettini et al (2017) and others, our findings are in agreement with other studies on E171 toxicity in which TiO_2 is incorporated into food such as the 2-year NTP bioassay (NTP, 1979). This calls into question the relevance of models in which E171 is administered in water or through oral gavage. Furthermore, animal models of human disease are often complicated and indirect, and their utility for toxicology testing is questionable.

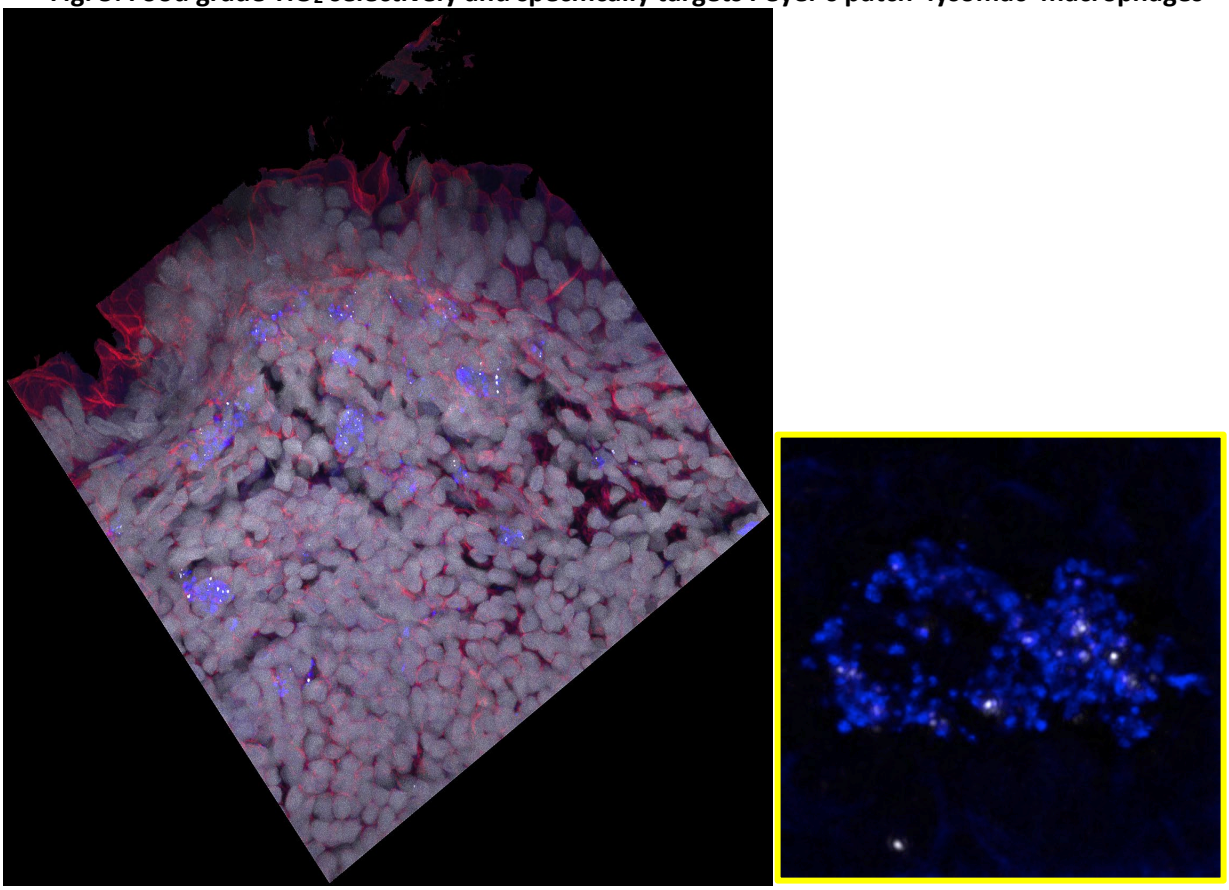
- ***TDMA's New Science Program for TiO_2 (Presented by D. Kirkland & D. Lockley)***

Two new projects that should help to fill some of the data gaps identified in the expert panel review of the genotoxicity of TiO_2 (notably new data on *in vivo* gene mutations) are planned and a further study mandated by the European Chemicals Agency (ECHA) also has to be conducted.

Firstly, it is proposed to investigate induction of gene mutations in transgenic animals (TGR study) according to OECD guideline 488. The oral route of administration will be used, but preliminary work will be conducted to optimise exposures according to delivery method (drinking water, diet or gavage dosing), and whether transgenic rats or mice are most appropriate. The tissues to be sampled for mutations will be those most routinely sampled, namely glandular stomach and duodenum (for site of contact effects), and liver (highest exposed internal organ and site of metabolism). In addition, bone marrow will be sampled to provide data from a peripheral, rapidly dividing tissue. Based on the other upcoming studies where other tissues will be studied (discussed below), samples of ileum, colon, testes, spleen, kidney and brain will also be sampled and frozen for possible later analysis. Blood samples will be taken at appropriate intervals for measurement of micronuclei in reticulocytes, and satellite animals will be treated, and blood sampled for measurement of TiO_2 exposures. The grades of TiO_2 to be tested in the main TGR study are not yet identified but could be determined from *in vitro* gene mutation tests on the 13 grades to be used in the lung comet study (see below). However, if such *in vitro* tests are not informative then at least E171 and P25 will be studied.

Secondly, research at the University of Cambridge has shown that TiO_2 is sequestered in high amounts in macrophages (lysomac cells) of Peyer's patches (ileum area of the small intestine) following dietary administration to mice (Fig. 5 kindly provided by Dr. John Wills).

Fig. 5: Food grade TiO_2 selectively and specifically targets Peyer's patch 'lysomac' macrophages



Such sequestering is also seen in human samples from cadavers, and from the study of Akagi et al. (2023) it appears that sequestering into Peyer's patches is also seen in rats. Whilst the lysomac cells do not divide, and therefore will not express mutations, or suffer any deleterious genotoxic effects, the cells that surround them can divide and could experience genotoxic damage (so-called "by-stander effects"). Frozen samples of Peyer's patches from treated and control mice are already available and could be investigated to see whether DNA damage using the γH2AX technique (detects double-stranded DNA breaks) occurs in these by-stander cells. If γH2AX lesions increase in "by-stander" cells of treated mice, then samples could be taken and analysed for presence of mutations, because DNA strand breaks may be repaired or be lethal and may not necessarily be converted to stable genetic changes such as mutations. The amounts of tissue available surrounding TiO_2-rich lysomac cells will not provide sufficient DNA for the TGR technique to be used. However, Duplex Sequencing (which is a version of a new technique called error-corrected next generation sequencing or ecNGS) requires much less tissue. If the DNA strand breaks do not lead to changes in mutational signatures, then it is highly likely they do not represent a direct genotoxic effect and may be secondary to other effects such as induction of oxidative stress. Duplex Sequencing could also be done in the animals treated in the TGR study (to compare transgenic and Duplex Sequencing results).

Finally, a study to measure induction of DNA strand breaks (comets) in lung following intratracheal instillation of 13 different grades of TiO_2 has been mandated by ECHA for REACH substance evaluation.

This is designed to select a smaller number of grades for full inhalation studies. Such a study would not be selected by choice, because it is a very challenging study for the following reasons:

- The numbers of TiO_2 grades to be tested.
- Dosing on 2 consecutive days
- Sampling lung tissue at 2-6 hrs, 24 hrs and 28 days after the 2nd dose
- Additional investigations to look for oxidative stress, tissue toxicity, changes in blood parameters, cardiovascular function, histopathology etc.

Because 3 concentrations of each grade of TiO_2 need to be included, together with negative (vehicle) controls, plus positive controls (standard and for oxidative damage), it is impossible treat the required 5 rats/dose for a single grade of TiO_2 on the same day at the same time, and thus treatment of the different dose groups for a single grade has to be split across different days. It is important, therefore, to control for day-to-day variability, and this will done by employing a "block design". Preliminary work has been on-going to identify which early sampling time (between 2 and 6 hours) is optimal and can be used in all parts of this study.

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E171's Unique and Unmatched Properties (presented by M. Tobyn)

As a material, E171, a form of titanium dioxide, has a wide range of properties which are advantageous to the pharmaceutical industry. E171 is purified and synthesized from specific ores and is only processed via one of the available routes for synthesizing titanium dioxide, one which does not have the residues associated with manufacture of titanium dioxide for industrial purposes. Pharmaceutical E171 is a specific polymorph of titanium dioxide, anatase, and is not a nano material.

The functionality of E171 comes from having a range of properties, many of which are associated with titanium dioxide's functionality as an inorganic material.

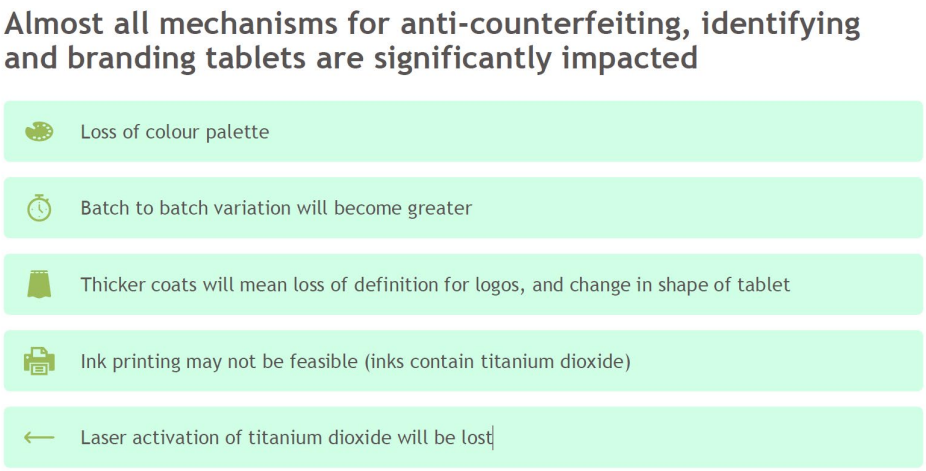
E171 has a high melting point, negligible solubility, no pH sensitivity and is not reported to have any chemical interactions with drugs or other excipients. It is an inert ingredient under pharmaceutical conditions. As a semi-conductor titanium dioxide has a band gap which absorbs UV light, promoting an electron in its structure. Separate from its ability to efficiently absorb UV, it has an unusually high refractive index, allowing it to disperse visible light. The material can also change color on laser irradiation, due to a change in oxidation state.

The particle size of E171 is a key contributor to its functionality in dispersing visible light. This material is not a nanomaterial by any agreed definition, but it does contain a large proportion of particles with a diameter of 100nm-200nm. This particle size, which encompasses particles with a size around twice that of wavelengths of visible light, is most efficient at dispersing visible light. Truly nano-sized titanium dioxide does not disperse visible light and is of no utility in pharmaceutical oral solid dosage forms.

This range of properties that E171 has means that it is ideal for protecting drugs from UV and visible light degradation, enables reproducible colors with luster and tone, and can be used in laser marking to facilitate precise images using its color change mechanism. Its optimum particle size means that it can achieve these effects at very low solids loading, meaning that films using the coat can be quickly and efficiently applied, without the solid E171 disrupting the film or making the system viscous or difficult to use.

A survey of the available materials which are proposed as potential E171 alternatives quickly reveals that none of them have the unique range of functionality which titanium dioxide demonstrates. None of the proposed materials have the combination of inert nature, high melting point and negligible solubility across the pharmaceutical pH range. If the material is not a semi-conductor, it cannot absorb UV radiation via the band gap mechanism. All of the proposed materials have a significantly lower refractive index than E171. None of them undergo a specific and reproducible color change in response to laser irradiation.

There is also a fundamental problem with respect to the particle size of these materials, in comparison to E171. As noted above the efficient dispersion of visible light is a function of having particles in a specific size range, which E171 does. Any material with significantly higher particle size will be markedly less efficient in dispersing visible light and will have to be used in significantly greater quantities than E171 when you also consider the much lower refractive index. However, if the replacement material does have optimized properties, i.e., in the 100nm-1µm diameter range, for dispersing visible light it will have been flagged for removal from the armory by the same mechanism which is threatening to delist E171 in some markets. Replacement of one material on the list with another that could be delisted is a fruitless exercise.



From a materials science perspective it is not expected that any of the materials proposed as alternatives to E171 would be expected to have the functionality of E171 and will have to be used in much higher quantities even to have some of the functionality.

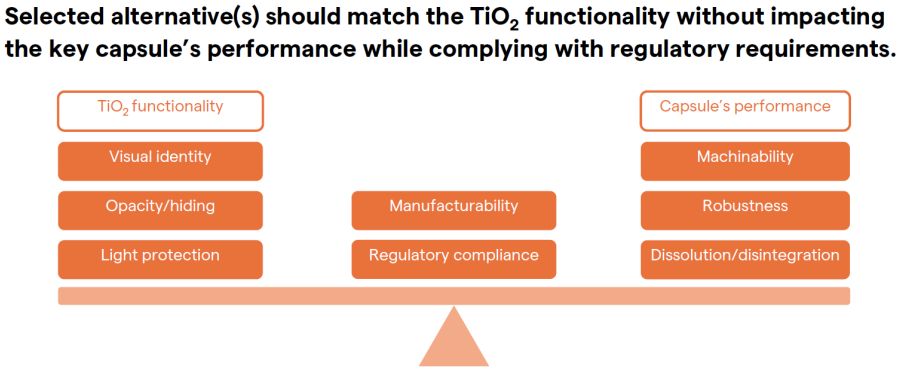
Supplier's Technical Challenges in Replacing E171 in Film Coating and Capsule Shells (presented by K. Hughes and B. Baert)

Collaboration between seven global film coating suppliers concluded replacing E171 will be difficult and time consuming especially since it is known that titanium dioxide is safe to use. These suppliers are all

working diligently to help their customers navigate the industrywide technical challenges of substituting E171 in pharmaceutical film coatings. While each supplier presented formulation challenges and solutions in their own unique way, there was agreement on the major areas of concern:

- A replacement for E171 that offers the opacity, whitening power and regulatory acceptability of E171 has yet to be identified.
- Excipients such as calcium carbonate, talc, kaolin, starches, and sugars can provide some opacity in film coatings but will need to be applied at higher application levels to achieve the same opacity as an E171 containing film. This means that for darker substrates, a substantially higher application of film may be needed to provide a uniform color coating.
- Color matching existing E171 containing film coatings is difficult because replacement of the white pigment from the film with an opaque but non-white alternative will cause the other pigments (Lakes, iron oxides, natural colors) to become more intense at much lower inclusion levels.
- Finally in contrast to regular E171 based film coating systems, the final film coating appearance of a titanium dioxide free formulation can be impacted by the equipment and the equipment scale. Removal of E171 gives outsized influence to the other film coating ingredients effect on dosage form appearance, removal also narrows process parameter flexibility.

E171 has an important role in hard capsules. It helps to create a visual identity unique to the product and ensures full masking of the capsule shell contents. It also protects ingredients that are susceptible to light degradation. The whiteness and opacity can be obtained by using relatively small amounts of E171, which allows the structural integrity of the polymeric film to be maintained. This results in robust capsules shells that are not brittle and that perform well in terms of machinability and disintegration performance.



If E171 can no longer be used, there are different options:

- Uncolored transparent capsules or capsule colored using soluble dyes can be used as alternatives. A broad color offering is still possible, but light protecting and masking will be lost.
- E171 can be replaced by iron oxides. Depending on the type of iron oxide used and the amount present in the formulation, iron oxide containing capsules can be semi-opaque or opaque. Moreover,

iron oxides can also give reasonable protection against UV and visible light. Although a wide color palette can be obtained, no white color is possible and also no exact match with a E171 containing formula will be possible.

If white opaque capsules are desired, alternative opacifying technologies that are equivalent or identical to E171 are needed. Such alternatives should have the same functionalities as E171:

- They should provide excellent whiteness.
- Provide full masking properties and protect from both UV and visible light.
- The capsule performance should not be impacted: capsules must still perform well on high-speed filling machines, should not be brittle and should have excellent disintegration characteristics. All of this should be balanced with good manufacturability and with regulatory compliance.
- Calcium carbonate ($CaCO_3$) is listed as a food colorant in Europe. However, to maintain good robustness, machineability and disintegration performance, whiteness and opacity are compromised. Adding more $CaCO_3$ to compensate for the reduced whiteness and opacity is not possible as the capsule would become brittle. Increasing the thickness of the polymeric film is also not an option as deviating from the predefined strict dimensional specification would mean that manufacturability and machineability would be impacted.
- Using a combination of tetrasodium pyrophosphate and trisodium phosphate, Lonza was able to create white capsules that are equivalent to and E171 containing capsule. However, both salts are not listed as food colorants. As this is a requirement for colorants to be used in medicinal products, the use of these salts as alternative colorant/opacifier comes with regulatory challenges.

In conclusion: there are various solutions, each with their strengths and opportunities but there is currently not a one-on-one match for E171. General capsule performance can be maintained, but either the colorant functionality is impaired, or the regulatory acceptance is jeopardized. Having E171 alternatives that are applicable across the board will require joint efforts of capsule manufacturers, capsules users and regulators.

Experiences in Pharmaceutical Drug Products Using E171 Alternatives (presented by J. Melnick)

In film coated tablets, E171 is typically present at levels of 10-30% in the film coating formulation which for adult products typically accounts for 2-3% of the total tablet weight. In hard capsule shell formulations E171 is typically found in the capsule shells at levels ranging from 2-5% based on empty capsule weight. The following examples show some of the difficulties encountered by using the currently available replacements for E171 in film coatings and hard capsule shells in an effort to color match and obtain a pharmaceutically elegant product by replacing titanium dioxide with other opacifiers and colorants.

Small scale coating evaluations were performed using several different film coating colors and systems. These evaluations were conducted manufactured using the color mixture suppliers' recommendations for suspension preparation and coating conditions. The results from the coating mixture studies showed that direct quantitative replacement of E171 with calcium carbonate or calcium carbonate and isomalt did not allow for a similar appearance in the dosage form, tristimulus $dE^* < 2$ (Hetrick), when compared to its E171 containing counterpart regardless of weight gain, Table 2. The table shows the point where

the weight gain achieved a dE* value <2, i.e. comparison to previous weight gains taken at ~1% weight gain intervals, signifying that the color of the tablet was no longer changing with additional coating being applied. The tablets where a dE* <2 was obtained were then compared to their E171 containing counterpart at a weight gain level of 3% to 4%w/w. In all of these evaluations the color of the dosage form was not considered similar to its E171 counterpart.

Table 2. Color evolution of various color mixtures

Film Coating Color	Film Coating Polymer System	Film Coating Opacifier/Colorant	Weight Gain where dE* to previous weight gain falls below 2	dE* to Titanium Dioxide Counterpart
Blue	Hypromellose	Calcium Carbonate	dE* < 2 not achieved up to 8%	Not Applicable
Blue	Hypromellose	Calcium Carbonate / Isomalt	4%	8
Light Yellow	Polyvinyl Alcohol	Calcium Carbonate	5%	31
Yellow	Hypromellose	Calcium Carbonate	dE* < 2 not achieved up to 8%	Not Applicable
Yellow	Hypromellose	Calcium Carbonate / Isomalt	4%	11
Biege	Polyvinyl Alcohol	Calcium Carbonate	7%	24

Alternative film coatings which contained just calcium carbonate resulted in significant color variation within an individual tablet. The appearance of the color of the belly band and the concave surface of a tablet were different resulting in the lack of a pharmaceutically elegant dosage form. Figure 6. The alternatives containing a combination of calcium carbonate and isomalt showed better color uniformity within an individual tablet, but overall appearance resulted in a speckled or mottled appearance which did not change with additional applied coating amounts, Figure 7 again lacking pharmaceutical elegance.

Figure 6. Color variation observed within individual tablets

Figure 7. Comparison of Calcium Carbonate (left) and Calcium Carbonate with Isomalt (right) at 2% Theoretical Weight Gain

The use of a hypromellose based coating system with calcium carbonate showed poor adhesion to the debossment used in the tablet evaluation, Figure 8. Other areas within the tablet surface, i.e. land, belly band, etc, did not show any signs of reduced adhesion to the tablet surface when cross-sectional analysis of the tablet were conducted. These observations around reduced coating adhesion were not present the hypromellose with calcium carbonate and isomalt or the polyvinyl alcohol systems.

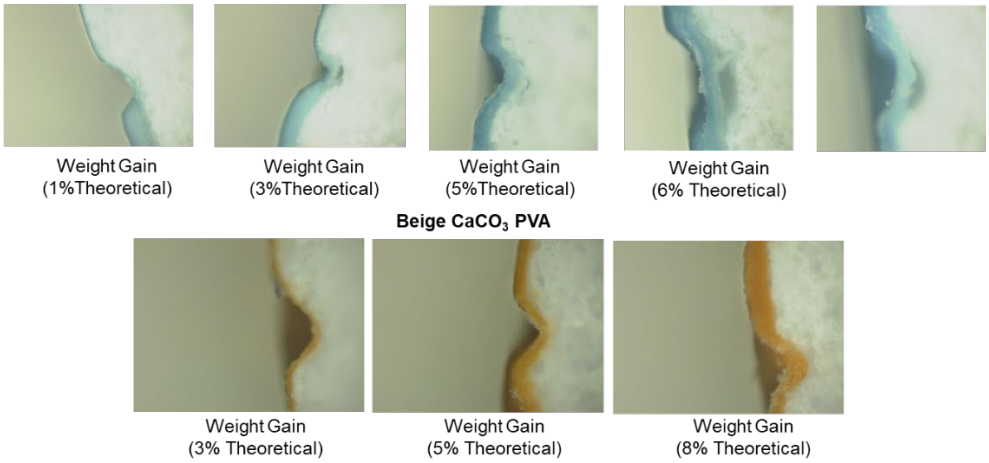


Figure 8. Adhesion difference between hypromellose and polyvinyl alcohol-based coating systems

Studies were conducted using microscopy were performed to evaluate the surface appearance/texture when using the alternative solutions in comparison to their E171 counterpart. Figure 9 shows an example the surface differences at an applied 5% weight gain using similar thermodynamic coating conditions. As can be seen in the photos the use of calcium carbonate and calcium carbonate with isomalt results in a different appearance and surface texture.

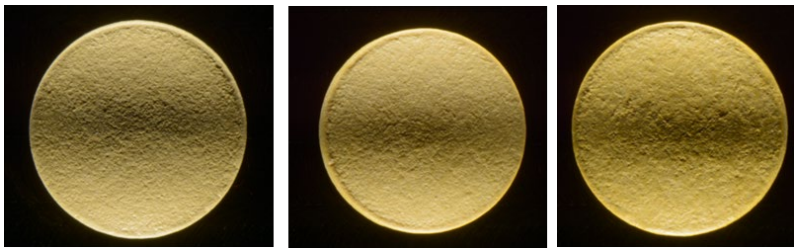


Figure 9. Coated Tablet Surface Appearance E171 (left), Calcium Carbonate (middle), Calcium Carbonate / Isomalt (right)

Capsule shells were evaluated for opacity and blinding capability since they are heavily utilized in clinical trials. Much like with coating mixtures, calcium carbonate is the leading solution for opacifiers to replace E171. However, due to the difference in opacity, the calcium carbonate capsule regardless of capsule polymer film system results in capsules that are quite transparent, Figure 10. These capsules would not allow for proper blinding of the capsule shell contents and also increase the risk of having stability issues for photolabile fill materials. As previously shared, Lonza currently has solution for gelatin capsules which utilizes tetrasodium pyrophosphate and trisodium phosphate as opacifiers. The use of these materials results in a capsule with opaqueness similar to that of a E171 containing gelatin capsule, Figure 11. This specific capsule shell has just been recently launched and much like the calcium carbonate containing capsule shells, there is limited data on the mechanical integrity, stability and ability to add colorants to this capsule shell. Another option to afford opaque capsule shells would be to use iron oxides as an opacifier. Using iron oxides does bring on an additional burden, depending on size of the capsule, number of units required to achieve the desire dose could result in a regulatory implication because of the amount of iron consumed.

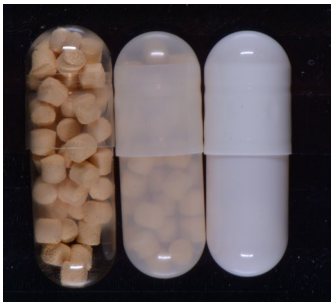


Figure 10. Hypromellose Capsules, No Opacifier (left) Calcium Carbonate (middle), E171 (right)

Figure 11. Gelatin Capsule: E171 (left) Alternative Opacifiers (right)

E171 plays a critical role in marking individual dosage units when used for the production of white or light-colored imprinting inks. In addition, the pharmaceutical industry has adopted using UV laser marking of tablets and capsules that contain E171 to afford a cleaner appearance which also results in the ability to add more detail aiding in the prevention counterfeit drugs. Removal of E171 would then eliminate the possibility of using either of these options when designing a dosage form that allows for a patient, health care provider or emergency responder, etc., to quickly identify medicines.

Based on these experiences with the currently available solutions for film coatings and hard capsule shells it is anticipated that there will be a reduction in product quality with respect to the physical and/or the chemical attributes of the solid oral dosage forms even if one is not trying to color match an existing marketed product. Currently, there are no proven platform alternatives currently available for film coatings or capsules shells. These findings were in alignment with the technical challenges described by the film coating and capsule shell suppliers.

Impact of Using E171 Alternative on Specifications and Formulation Bridging (presented by A. Abend)

As with any “post approval change”, the impact a ban of E171 and its removal from film coatings or capsule shells on pharmaceutical product quality attributes would need to be assessed on a case-by-case basis (EMAs letter to EC (2022)). The outcome of the overall product specific quality risk assessment, manufacturing, and supply chain considerations, may lead a company to decide to remove the film coating or hard capsule shell (not feasible), remove only titanium dioxide from the film coating or capsule shell formulation, or remove titanium dioxide in entirety and replace with an alternative opacifier that is approved for use in pharmaceutical products.

Removing the film coating or just removing E171 from the film coating or capsule shell will at a minimum impact the appearance specification. Other specifications (i.e., assay, uniformity of dosage units, dissolution) are unlikely impacted and thus little to no analytical method revalidation is expected.

On the other hand, replacing E171 with an alternative opacifier that may be required either to mask potential core tablet discoloration or mitigate photodegradation may require that all product

specifications to be redeveloped and revalidated before the necessary manufacturing process evaluations can occur (engineering/pilot batches, stability studies, potential clinical trial materials "biobatch") that are then submitted to health authorities. Efforts to revalidate assay, impurity, and uniformity of dosage units are likely less challenging from a technical perspective but require significant resources if a company would have to change their entire portfolio of solid oral dosage forms that are affected. The impact on rate and extent of drug product dissolution may be different for the changed product which may cause a concern from an *in vivo* performance perspective.

If Europe were the only market that requires removal of titanium dioxide from pharmaceutical products, and if the resulting manufacturing change were to be considered a type 1a/1b variation by EMA, then a company must justify why no additional clinical bioequivalence (BE) studies with the approved ("REFERENCE") versus the reformulated ("TEST") products are needed to demonstrate that *in vivo* performance is not affected. On the other hand, companies first seek to demonstrate dissolution profile similarity in the approved Quality Control dissolution method as a surrogate of clinical BE. It is very likely that removal of titanium dioxide from tablets and capsules leads to dissolution profile dissimilarity however, in an unknown number of cases extensive BE studies would be required. Bridging E171 containing "REFERENCE" and "TEST" products in the EU following EMA's variations guidance (REF) may seem relatively straight forward, if dissolution similarity according to the guidance can be established successfully. Other markets following the EU's titanium dioxide ban are likely requiring companies to follow their own local guidance which are often different from the variation's guidance. This may lead to manufacturing changes being supported in some markets using *in vitro* data while in other markets BE studies would be needed. Given the high uncertainty of meeting regulatory requirements in markets where the changed product would be offered, companies may either proactively perform BE studies or withdraw the product from the market(s) that require BE when these studies are considered cost prohibitive. This situation may be even more complex for products currently in late-stage clinical development. Here a Quality Control specification has not been approved and *in vitro* bridging may be limited to multi pH media testing – with more dissolution profiles to assess, the likelihood of not passing similarity increases, leading to additional BE studies and potential product filing delays.

It is also very likely that the removal of E171 will require additional manufacturing process changes as outlined by the suppliers' recommendations. In these situations, companies may approach health authorities, when permitted, and ask for scientific advice. How EMA and other health authorities would handle a surge in scientific advice concerns the pharmaceutical industry as there's general anxiety that either the most conservative approach needs to be taken (i.e., several relative bioavailability or BE studies) or the timing of getting answers will be unpredictably long.

Replacing E171 with an alternative opacifier will require reassessment of product shelf life and storage conditions. Based on current industry experience, the alternatives require thicker film coating levels. Therefore, the environmental conditions for manufacture and storage of the product may need to be redefined. It is highly likely that for poorly soluble drugs using enabled technologies (i.e., amorphous solid dispersions), API changes that could impact bio performance. To mitigate the risk of product quality failure, packaging, and storage conditions (controlled temperature vs. store below room temperature), and reduced shelf life may be required. These measures would all complicate the overall product supply chain resulting in a company potentially marketing a product with two different quality profiles, one for countries allowing titanium dioxide and another with an alternative colorant/opacifier having a second and possibly lower quality when compared to its titanium dioxide counterpart. Moreover, these

additional variations will increase the content and thus type of post approval submission further impacting resources from companies and health authorities.

Challenges to Providing Essential Drugs if a E171 Ban Takes Place: Global and Generic Pharmaceutical Perspective (presented by B. Hancock and D. Cragin)

The many unique properties of E171 as previously described make it difficult to replace as an opacifier in solid oral medicines. For example, it is generally unreactive towards other formulation components and very low levels are needed for E171 to exert its light-protective effect. It is also widely available, well tolerated, and precedented in every global market.

Medicines for Europe, European Federation of Pharmaceutical Industries and Associations (EFPIA), and Association of the European Self-Care Industry (AESGP) are cooperating regarding assessing the impact of potential ban of E171. A 2020 survey of these organizations found that approximately 60% of oral dosage forms and 90% of colored/coated tablets use titanium dioxide, E171.

Pharmaceutical manufacturers have only a few options if the use of E171 in tablets and capsules shells is prohibited in Europe and allied markets. These include removal, replacement, and product withdrawal. Simple removal will result in a reduction in product quality in most cases, and there are no proven platform alternatives currently available.

The challenges for replacing E171 in medicines include:

- The lack of a long-term track record for the proposed alternatives.
- Third party suppliers provide most film coatings and capsule shells for prescription drug products. As such, medicines manufacturers are highly reliant on these 3rd party suppliers to innovate and develop E171-free alternatives. Many of these suppliers are small companies with limited capacity to develop alternative products in a short timeframe.
- There is limited pharmaceutical R&D and testing capacity to evaluate a significant number of alternatives to ensure quality product can be achieved.
- Moving away from a single global product formulation adds significant complexity and costs to the supply chain for most products.
- Many existing products will need to be reformulated at the same time and updating hundreds or thousands of regulatory dossiers in a short time is unprecedented.
- The regulatory steps required to approve a reformulated product are complex and slow.
- Patients may be confused by changes in the appearance of their medicines, and this could lead to reduced dosing compliance.
- Clinical research with patient groups suggests that changes to the feel and texture of oral dosage forms can lead to difficulties in swallowing and reduced palatability. In turn this can lead to missed doses or discontinuation of therapy which may cause poorer patient outcomes in the long term.

For new products, once the technical feasibility of using an E171-free formulation has been demonstrated it will be critical to establish the safety of any alternative materials used in the formulation. Then it will be necessary to assess the impact of changing formulation on ongoing clinical studies, manufacturing efficiency, cost of goods, and the global supply chain. It will also be necessary to

manufacture and supply both formulation variants (the current and the new formulation) until regulatory approval is gained again impacting the limited pharmaceutical R&D and testing capacity.

In addition to these challenges, marketed product transitions will require an in-depth understanding of the business, technical, medical, and technical risks associated with a change in formulation. Likely a staged approach over many years would be needed to ensure that the supply of medicines to patients is not disrupted.

Lastly, there are still many unknown factors to contend with which makes planning for a E171-free product portfolio very challenging. For example:

- Which other countries/regions may ban the use of titanium dioxide?
- Will existing commercial products be 'grandfathered in' or will they all need to be reformulated?
- What would be the timeframe for a transition to E171-free product?
- Under what circumstances might E171 still be needed or allowed for certain specialized medicines?
- What are the EMA's plans for approving large numbers (thousands) of updated MAAs in the event of a ban on the use of E171?
- How will large scale medicines shortages in Europe be prevented?

The ban will be particularly problematic for generic drugs. Based on publicly available information in Teva's ESG report, Teva's portfolio current has over 2000 drugs, many of which are oral solid dosage forms. The reformulation of thousands of products by the generic industry isn't practical.

If reformulation is required, each individual reformulation would cost 500,000 to 1.5 million Euros (without consideration of the EU manufacturing capacities required for EU only products). Reformulation would require extensive testing including an assessment if removal of E171 impact absorption during food consumption… on delayed release, on bioavailability in other ways, or change quality and stability. Each reformulation would be expected take 30-60 months and the thousands of drugs could not be completed all at the same time.

Drug shortages are already a problem in the EU and an E171 ban would make the shortages even worse. A 2022 survey of groups representing pharmacies in 29 European countries found almost a quarter of countries faced shortages of more than 600 drugs and 20 percent reported 200-300 drug shortages. Generic drugs are an essential aspect of providing affordable health care.

There is no feasible replacement for TiO2 that addresses the toxicological concerns of regulators and the functional needs for effective pharmaceuticals from a drug manufacturers perspective.

Summary & Conclusions

In June 2023 the Product Quality Research Institute (PQRI) 2-day workshop discussed why titanium dioxide (TiO_2) should not be banned for use in pharmaceuticals. Many world-class experts presented information on the safety and the current global regulatory assessments of TiO2 as well as the challenges when attempting to use the available TiO2 alternatives in drug formulation. The details of these presentations were outlined in the body of this paper and the key conclusions are provided below.

For decades TiO_2 has been used widely in cosmetics, medicines and foods due to its safety and utility. Food-grade TiO_2 (known as E171) was recently banned for use in foods and dietary supplements in the European Union (EU), and, according to EU law, there is a potential that TiO_2 could also be banned there as well in pharmaceuticals as early as 2025. As an estimated 91,000 drug products in the EU contain titanium dioxide, and a ban on its use could have a significant impact of the availability of drugs for patients in Europe, but as a consequence, possibly worldwide.

Titanium dioxide has unique performance qualities, beyond being a colorant, required in solid oral dosages including opacity (protection from UV light) and the ability to protect printing elements on tablets and capsules. No other excipient that might serve as a direct replacement could perform an equivalent function in either the capsule shell or the tablet coating. In addition, even if a direct replacement were found, reformulation of ***each*** drug product would take 30-60 months and require a large investment of resources, possibly also involving new stability and bioavailability studies. Similarly large resources would be required in the registration, approval and launch of each reformulated drug product. This would result in many drugs becoming unavailable in the EU and exacerbating current drug shortages.

Most importantly, there isn't a safety reason to trigger this change. Despite the fact that there were no studies showing direct interaction of E171 with DNA, the European Food Safety Authority (EFSA) concluded in 2021 that a genotoxicity concern could not be ruled out and that E171 could no longer be considered safe in food. However, in assessing the potential health effects of E171, EFSA based its evaluation on studies in which laboratory animals were exposed in ways that are not reflective of human food exposures, such as sonication in water. They also appear not to have rigorously evaluated the biological relevance of the test systems, the robustness of the study designs or the reliability of the data. Rather than do a formal risk assessment, EFSA did a hazard evaluation that focused on TiO_2 nanoparticles which were not representative of E171 or relevant for assessing E171 as a food additive.

In light of EFSA's concerns for genotoxicity, an independent panel of experts conducted a rigorous weight of evidence review of the genotoxicity of all grades and sizes of TiO_2 (published in Kirkland et al., 2022). The panel approach was different from that of EFSA, excluding certain studies that are only indicator tests, and evaluating the robustness of the study designs and the reliability of the data. The panel concluded that the existing evidence from reliable, relevant and robust tests does not support a direct DNA damaging mechanism for TiO_2 (nano and other forms). However, more confident conclusions could be reached if there were more robust data on relevant endpoints (e.g. *in vivo* gene mutations) and mode of action, and such studies are planned.

In addition, after the PQRI conference, Japan's Ministry of Health, Labour and Welfare (MHLW, 2023) published a study that specifically addressed the potential concern for genotoxicity with TiO_2 nanoparticles. Studies in rats using 6 nm TiO_2 nanoparticles at doses up to 1,000 mg/kg/day, i.e., equivalent to 50 grams/day for a person found no preneoplastic changes or evidence of genotoxicity. In addition, there are no consistent, reliable studies showing an effect

on the immune system. Furthermore, many regulatory agencies have now concluded the safety of TiO_2. Food Safety Australia/New Zealand (2022), Health Canada (2022), JECFA (2023) and US FDA (2023) have all concluded TiO_2 does not present a genotoxic hazard in vivo. These conclusions are crucial since the exposure of concern for people is in vivo. Considering these conclusions and that a form of TiO_2 equivalent to E171 tested negative in an oral carcinogenicity study (NCI, 1979) at the maximum dose possible, i.e., 5% of the diet, which is equivalent to 2,250 mg/kg/day or 112.5 grams/day for a 50 kg person, no genotoxic risk to people would be expected whether TiO_2 is ingested from food, or from medicines where the exposures are orders of magnitude lower than food.

The suppliers of film coating systems and capsule shells have shown that finding a replacement to E171 which has similar opacity, whitening power and regulatory acceptability will be difficult. In addition, there are other unique and unmatched attributes that titanium dioxide affords which the alternatives do not have, e.g., inert nature, high melting point, negligible solubility across the pharmaceutical pH range and ability to undergo a specific and reproducible color change in response to laser irradiation. The suppliers' observations have been confirmed by the pharmaceutical industry as they have evaluated the currently available E171 alternative film coating systems and capsule shells. In the end there is no workable replacement for E171 that meets the functional needs of the pharmaceutical industry and the toxicological concerns of the regulators.

In summary, there really is no significant safety risk to the use of TiO_2 (such as E171) in pharmaceuticals and therefore no case for a ban. However, there will absolutely be significant unintended, but predictable consequences to public health if TiO_2 were to be banned for use in these applications due to the associated drug shortages which would occur. There is a significant benefit to the continued use of TiO_2 in pharmaceuticals that has been demonstrated in the information contained in this paper and that must be weighed appropriately in deciding whether to extend the ban of E171 to pharmaceuticals.

Post Workshop Note on Recent Japanese MHLW and JECFA Regulatory Opinions which support safe use of TiO_2.

After the PQRI Workshop was held, additional reports concerning TiO_2 safety were published which also support the safe use of TiO_2 in foods (and pharmaceuticals). For example, in Japan, the MHLW has conducted additional studies on nano grades of TiO_2 to further assess whether there are any genotoxicity concerns and they have determined that they do not have any significant concerns regarding the safe use of TiO_2 in foods. Based on the results of the Akagi study and the outcomes of many other global regulatory authority's reevaluation of TiO_2 safety, MHLW sees no significant genotoxicity uncertainties that would indicate a safety concern with TiO_2.

JECFA recently published a summary report (24 November 2023) on their new risk assessment of titanium dioxide. JECFA noted that TiO_2 was poorly absorbed from the gastrointestinal tract and that the oral bioavailability of TiO_2 in humans is very low. JECFA furthermore considered that no evidence for carcinogenic, reproductive or developmental toxicity effects after long term exposure in animals have

been identified. JECFA also noted that there are currently no epidemiological studies that allow any conclusions to be drawn with respect to any association between dietary exposure to TiO_2 and human health effects.

After reviewing the available scientific literature JECFA noted limitations in the available evidence for genotoxicity. JECFA emphasizes that the OECD guidelines for investigating genotoxicity have been developed and validated for chemicals, and that they may not be easily applicable without adaptations for testing poorly soluble particulate matter such as TiO_2. Recognizing the limitations and some equivocal findings in the available data on genotoxicity JECFA noted that the available data did not provide convincing evidence of genotoxicity for TiO_2.

JECFA reviewed all available research on genotoxicity risk and determined that the evidence is insufficient, owing mostly to the lack of suitable testing methodologies for nanoparticles. JECFA stated that they need more research to address the current uncertainty about the distribution of TiO_2 particle sizes in food and to develop genotoxicity tests that are more appropriate for nanoparticles.

In light of the very low oral absorption of INS171, and in the absence of any identifiable hazard associated with TiO_2 in the diet, **the JECFA reaffirmed the ADI "not specified" established in 1969**.

JECFA has previously evaluated titanium dioxide back in 1969, when JECFA concluded that the use of TiO_2 as a food additive does not pose a safety concern and therefore allocated an ADI of "not specified" under conditions of Good Manufacturing Practices (GMP). **This ADI has now been reaffirmed and should be the basis of global safety assessments of TiO_2 going forward.**

References:

- Jun-ichi Akagi, Yasuko Mizuta, Hirotoshi Akane, Takeshi Toyoda and Kumiko Ogawa. Oral toxicological study of titanium dioxide nanoparticles with a crystallite diameter of 6nm in rats. Particle and Fiber Toxicology volume 20, Article number: 23 (2023) https://particleandfibretoxicology.biomedcentral.com/articles/10.1186/s12989-023-00533-x)
- Report: Evaluation of Food Additive Titanium Dioxide. Food standards Examination Division, Health and Human Hygiene Bureau, Ministry of Health, Labour and Welfare of Japan (MHLW), 19 July 2023
- Joint FAO/WHO Expert Committee on Food Additives risk assessment of titanium dioxide risk released – background information, 24 November 2023 https://www.who.int/publications/m/item/jecfa-risk-assessment-of-titanium-dioxide-risk-released-background-information

Recommendations for Medicines and Healthcare Regulators

The information provided at the PQRI Workshop and summarized in this paper show that there are no significant safety concerns with the use of TiO2 (E171) in food or pharmaceutical products. This has been the conclusion of several other global regulatory agencies as well as JECFA who have all decided that no action is needed to limit the existing uses of TiO2 that are allowed at this time in each of their markets.

Additional data have become available and data-based scientific assessments have been done by world-class experts since the EFSA Opinion was published and it is clear that the EFSA Opinion has not been confirmed by other international reviews, possibly because they did not consider compelling and appropriate data on grades of TiO_2 that are relevant to the use of E171 in foods. A different type of assessment is needed when evaluating any material for use in pharmaceuticals where risk and benefit must be assessed in a patient-centric risk assessment model. Therefore, the EFSA Opinion which was focused on food uses and uses the "precautionary principle" is not the appropriate basis for a decision on the use of E171 in pharmaceuticals.

As has been outlined in this paper, there are currently no good alternatives to the use of E171 in pharmaceuticals that can provide equivalent performance and quality of drug products. Therefore, if a ban of E171 were to be extended to pharmaceuticals in 2025, many drug products will have to be reformulated leading to products of inferior quality and performance. If they cannot be reformulated into equivalent products of acceptable quality, they will need to be taken off the European market. The impact on patient compliance and therapeutic outcomes could also be significant due to differences in product appearance. In many cases, there will be no economic justification for reformulation, even if it might be technically possible, and this also will lead to many drug products being withdrawn from the European market. This will leave many EU patients without access to the drugs they desperately need. Significant drug shortages **WILL** occur if E171 is banned from use in pharmaceuticals!

As stated above, there really is no significant safety risk to the use of E171 in pharmaceuticals, however, there will absolutely be unintended, but predictable consequences to public health if E171 were to be banned for use in these applications due to the associated drug shortages which would occur. There is a significant benefit to the continued use of E171 in pharmaceuticals that has been demonstrated in the information contained in this paper and that must be weighed appropriately in deciding whether to extend the ban of E171 to pharmaceuticals.

All experts involved in the PQRI Workshop and who are authors of this paper recommend that EMA strongly support the continued use of E171 in pharmaceuticals in their proposal to the European Commission in April 2024.

Author/Speaker Biographies

David Schoneker – Black Diamond Regulatory Consulting, LLC/IPEC-Americas

David R. Schoneker is currently the President/Owner of Black Diamond Regulatory Consulting, LLC, a consulting firm specializing in providing regulatory and quality consulting for the pharmaceutical, dietary supplement, food and related industries. Prior to August 2019, David R. Schoneker was the Global Regulatory Director – Strategic Relationships at Colorcon, Inc. His responsibilities included global coordination of Colorcon's worldwide regulatory activities.

Colorcon is one of the world's leading excipient companies supplying coatings for pharmaceuticals which utilize titanium dioxide as a key ingredient. From 1995 to 2018 he was Director of Global Regulatory Affairs. Prior to 1995 he was Director of Quality Assurance and Quality Control where he coordinated all quality activities for Colorcon North America.

David was one of the founders of the International Pharmaceutical Excipients Council (IPEC) in 1991 and has chaired many activities for this group over the years related to excipient safety, quality and regulatory affairs. He currently is IPEC-Americas key representative on the IPEC/IQ Consortium TiO2 Working Group and acts a coordinator of various industry TiO2 groups.

David Kirkland - Kirkland Consulting - Genetic Toxicology Consultant

Professor Kirkland has a BSc (microbiology) from the University of London and a PhD (cellular cancer studies) from Brunel University. Following 2 post-doctoral fellowships he became Research Director at Toxicol Laboratories. He then joined Microtest Research Limited in 1984, which became part of Covance where, over 25 years, he was Head of Genetic Toxicology, Vice-President of Toxicology and of Scientific and Regulatory Consulting. In 2009 he became an independent consultant. He has extensive experience with regulatory issues relating to genotoxicity data, has published >150 peer-reviewed papers and is a regular podium speaker/chairperson.

He was awarded a Fellowship of the UKEMS in 2002, and made Honorary Professor of the University of Wales, Swansea in 2006. In 2010 he received the first Industrial Genotoxicity Group (UKEMS) Distinguished Toxicologist Award, and also the US Environmental Mutagen Society Alexander Hollaender Award for global leadership in the regulation of genetic toxicology testing. In 2014 he was awarded The Kitashi Mochizuki Award by the Japanese Environmental Mutagen Society for promotion of international harmonization of genotoxicity tests through the International Workshops on Genotoxicity Testing (IWGT) of which he was chair of the steering committee for 20 years, in 2015 he received the Jim Parry Award from UKEMS, and in 2022 he received the Frits Sobels award from the European Environmental Mutagenesis and Genomics Society.

For many years he was Special Issues Editor for Mutation Research and editorial board member of the Journal of Applied Toxicology. He was a member of the UK Government Advisory Committee on Mutagenicity for 10 years, was UK expert to OECD for genotoxicity guidelines, and Past President of the European EMGS.

David Cragin – Teva

Dr. Dave Cragin, DABT, is Senior Director of Product Science in Environment, Health, Safety and Sustainability at Teva Pharmaceutical. He contributes to the overall leadership of EHS&S functions and also leads a team that creates safety data sheets and occupational exposure limits to support efforts to protect employee safety and acceptable daily exposures for quality operations. He's also a subject matter expert on beta lactams, titanium dioxide, and iron oxide. Previously he served as a Director in Quality Assurance and multiple other roles for Merck & Co., Inc.

Outside of Teva, he teaches risk assessment and critical thinking for the Peking University, and Beijing Normal University. In addition, he has taught risk communication across the globe. He speaks Chinese and is knowledgeable in many languages. Dr. Cragin is a Trustee of the Toxicology Education Foundation, is Past-President of the Mid-Atlantic Society of Toxicology, and a Councilor for the Philadelphia Association for Critical Thinking. He received his Ph.D. in Pharmacology and Toxicology from University of California, Davis, his B.S. in Zoology from the University of Rhode Island, and is a Diplomate of the American Board of Toxicology.

David Lockley – Venator/TDMA

David Lockley works at Venator, formerly the Pigments and Additives Division of the Huntsman Corporation and provides global support to the business on toxicological and product stewardship issues for its new and existing products. He also provides technical (scientific) leadership to industry-wide trade associations, consortia and task forces involved in human health research, risk assessment, and regulatory agency interaction.

David is the Chair of the Titanium Dioxide Manufacturers Association (TDMA) Scientific Committee and Regulatory Task Force. After receiving his undergraduate degree in Biomedical Sciences from the University of Sunderland, David obtained a MSc in Toxicology from Birmingham, PhD in Biochemical Toxicology from Newcastle and Post Doctoral Studies in Molecular Toxicology from Dundee. He has been a European Registered Toxicologist (ERT) since 2008 and is a member of the British Toxicology Society (BTS).

David has over 15 years' industrial experience working as a toxicologist in the Pharmaceutical, FMCG, Chemical, Retail and Consultancy sectors in the UK.

Samuel M. Cohen, M.D., Ph.D., Department of Pathology, Microbiology, and Immunology and Buffett Cancer Center, University of Nebraska Medical Center,

Dr. Cohen has been involved in nearly 60 years of chemical carcinogenesis research, with over 480 publications in peer-reviewed journals and has written more than 50 chapters in various publications.

He is Board certified in anatomic and clinical pathology and is is the Havlik-Wall Professor of Oncology in the Department of Pathology, Microbiology, and Immunology and in the Buffett Cancer Center at the University of Nebraska Medical Center in Omaha, Nebraska.Dr. Cohen has won numerous honors and

awards such as the Lehman award and Merit award from Society of Toxicology, and is an elected fellow of IATP, AAAS, and member of Academy of Toxicological Sciences.

He serves on numerous national and international committees, editorial boards (including Toxicologic Pathology), and is a reviewer for numerous journals and granting organizations (including NIH, EPA, DOD). He also serves on the Expert Panel for evaluation of flavor ingredients.

Lance Blevins - Institute for Integrative Toxicology, Michigan State University

Lance received his BA in biology from the University of North Carolina at Chapel Hill where he conducted undergraduate research in a BSL3 laboratory setting. He then entered graduate school where he pursued his PhD in microbiology and immunology from Wake Forest University studying the regulation of virus-specific CD8+ T cell responses by invading bacterial pathogens.

After earning his PhD, Lance then joined Dr. Norb Kaminski's laboratory at Michigan State University as a post-doctoral research fellow, where he has made significant contributions to the field of aryl hydrocarbon receptor immunotoxicity. Lance was promoted in 2020 to the position of assistant professor with the institute for integrative toxicology at Michigan State University where he currently conducts research into the biological role of aryl hydrocarbon receptor in B cell subsets.

Dr. Blevins has over 10 years of experience in conducting hypothesis driven investigative research directed at elucidation of the cellular and molecular mechanisms by which pathogens and chemicals alter immune responses. These immunologic and immunotoxicologic studies have employed approaches spanning measurements of immune function in vivo, ex vivo and in vitro and Dr. Blevins has published research using murine, rat, non-human primate, as well as human model systems to study immune regulation and pathogenesis.

Mike Tobyn - Bristol Myers Squibb

Mike has worked for BMS for 18 years and is part of Materials Science and Engineering function within Drug Product Development (Product Development and Supply. His team is based in Moreton, England and New Brunswick, New Jersey. Their function is to look at all small molecule assets, from Discovery through to Manufacturing, and assess the characteristics, and using data to predict and understand their performance in solid oral dosage forms. The work involves analytical science and big data analysis, and Mike has co-edited book on the use of Multivariate Data Analysis in the Pharmaceutical Industry.

Mike has worked extensively in the area of excipients, and is a member of the USP Committee on excipient test methods, and is an advisor to the Handbook of Pharmaceutical Excipients. He is currently looking at mitigation strategies relating to the potential ban in European pharmaceuticals of titanium dioxide, which is in all BMS small molecule formulations, and 91,000 other pharmaceuticals across Europe. Mike is coordinating a cross industry technical response.

A Registered Pharmacist, Mike trained in Pharmacy at the University of Strathclyde, and took his PhD there in 1994. Mike taught Pharmaceutical Technology at the University of Bath and at the University spin-out company Vectura, where he was with the company from inception through to IPO.

In 2019 Mike was elected as the Eminent Fellow of the Academy of Pharmaceutical Sciences for his contribution to the field of Pharmaceutical Technology across the world.

Kevin Hughes - Colorcon

Kevin has been with Colorcon for over 18 years where he has been the Technical Expert in film coating, immediate release and extended-release excipients. Kevin is now Regulatory Affairs and Quality Assurance Manager for Colorcon and is responsible for the EMEA region, providing regulatory support to customers in both the pharmaceutical and food industries, monitoring any regulatory changes, industry initiatives and is closely involved with the IPEC Quality and Regulatory Affairs Committee. Kevin is also responsible for Quality at the Dartford site, and hosting all customer and certification audits as well as conducting supplier audits as an IRCA qualified Lead Auditor.

As subject matter expert Kevin is responsible for the paediatric initiatives within Colorcon and to update the organization about paediatric regulations, guidelines and the industry perspective.

Kevin is on the board of IPEC, actively participates in the IPEC Quality and Regulatory Affairs committee and also represents IPEC on the board of EUPFI (European Pediatrics Formulation Initiative). Kevin is also Vice-President of IPEC Federation.

Prior to joining Colorcon Kevin spent 5 years at Boots Healthcare Development, where he was Team Leader developing solid oral dosage forms for Boots Pharmacies.

Kevin graduated with a BSc (Hons) degree in Food Science from Nottingham University in 1994. He has been involved in the pharmaceutical industry for 22 years. Over this time he has built up a strong level of expertise in the development and manufacture of solid oral dosage forms.

Bram Baert - Lonza

With a PhD in Pharmaceutical Sciences obtained from the Ghent University Drug Quality & Registration laboratory, Bram developed a special interest in regulatory compliance.

After working 5 years in a product-oriented quality team with responsibilities concerning registration, validation and implementation at Pfizer Manufacturing Belgium, Bram joined Lonza / Capsugel about 7 years ago covering regulatory affairs for empty capsules in the EMEA region.

Jason Melnick - Eli Lilly and Company

Jason Melnick is a Senior Director at Eli Lilly and Company where he has worked for 26 years. He is a member of the global Technical Services and Manufacturing Sciences group supporting the development, technical transfer, and manufacturing of solid oral dosage forms. Jason has extensive experience using titanium dioxide as an opacifier and colorant for pharmaceutical coating applications along with its use in hard gelatin or hypromellose capsules shells. He currently co-chairs the International Consortium for Innovation and Quality in Pharmaceutical Development Titanium Dioxide Working Group.

Andreas Abend - Merck and Co., Inc.

Andreas Abend received his PhD degree in Organic Chemistry from the University of Karlsruhe in Germany. Prior to joining Merck and Co., Inc. as a Senior Project Chemist, Andreas spent 3 years as a Post-Doctoral Fellow at the University of Wisconsin's Enzyme Institute. He is currently a Senior Principal Scientist in the Biopharmaceutical Sciences group in MRL's Development Sciences and Clinical Supply Department.

Throughout his career at Merck and Co., Andreas provided analytical support to small molecule API and drug product development activities spanning all clinical phases. Over the last two decades, he and his team contributed to the more than a dozen new Market applications.

Andreas is a member of Merck and Co.'s Biopharmaceutical Advisory Team, co-chair of PQRI's BTC, and a member of IQ's Analytical Leadership Group. He presented at many national and international meetings, published several manuscripts on Clinically Relevant Dissolution specifications, photostability and impurity identification. In 2017 and 2019 he was a co-organizer of workshops at the Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI) and he is currently co-organizing a PQRI workshop dedicated to pediatric formulation development (Nov. 2023).

Bruno Hancock - Pfizer

Bruno C. Hancock currently leads the global pharmaceutical materials science group at Pfizer Inc. He holds a bachelors degree in Pharmacy from the University of Bath, UK and a Ph.D. in Pharmaceutical Technology from the University of Bradford, UK. He held a post-doctoral research appointment at the University of Wisconsin and worked at ICI Pharmaceuticals (now Astra Zeneca) in the UK and Merck Frosst & Co. in Canada before joining Pfizer.

At Pfizer he has worked in the areas of formulation development (focused on spray dried dispersions), powder technology, pharmaceutical materials science, drug product process development & technology transfer, and computational drug product design. Bruno has supervised the research of students and post-doctoral researchers in Canada, the United States, and Europe. He has published over one-hundred-and-thirty full research papers and several patents.

He has served as an advisor to the United States Pharmacopoeia on the use and testing of pharmaceutical materials since 1995, and was the recipient of the Royal Pharmaceutical Society of Great

Britain Science Medal in 2000 for his contributions to pharmaceutical research. He was elected to Fellow status in the American Association of Pharmaceutical Scientists in 2004. He has been an Editor for the Journal of Pharmaceutical Sciences since 2014 and he currently serves as a co-editor for the Handbook of Pharmaceutical Excipients.