Applying Evidence-Based Approaches to Manage Titanium Dioxide as a Food Additive

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Introduction

- **Titanium Dioxide (TiO_2)**, also known as E171, is a mineral used for its bright white color and opacity.
- Widely utilized in food products (e.g., confectionery, dairy, baked goods) to enhance visual appeal.
- Also found in non-food applications such as cosmetics (e.g., sunscreens) and pharmaceuticals (e.g., tablet coatings).
- Recent studies have raised safety concerns, especially regarding nanoparticles.
- Diverse regulatory responses worldwide, reflecting varying approaches to managing **TiO_2** usage.

Sources of Exposure to TiO_2 in Food

Intentional Exposure

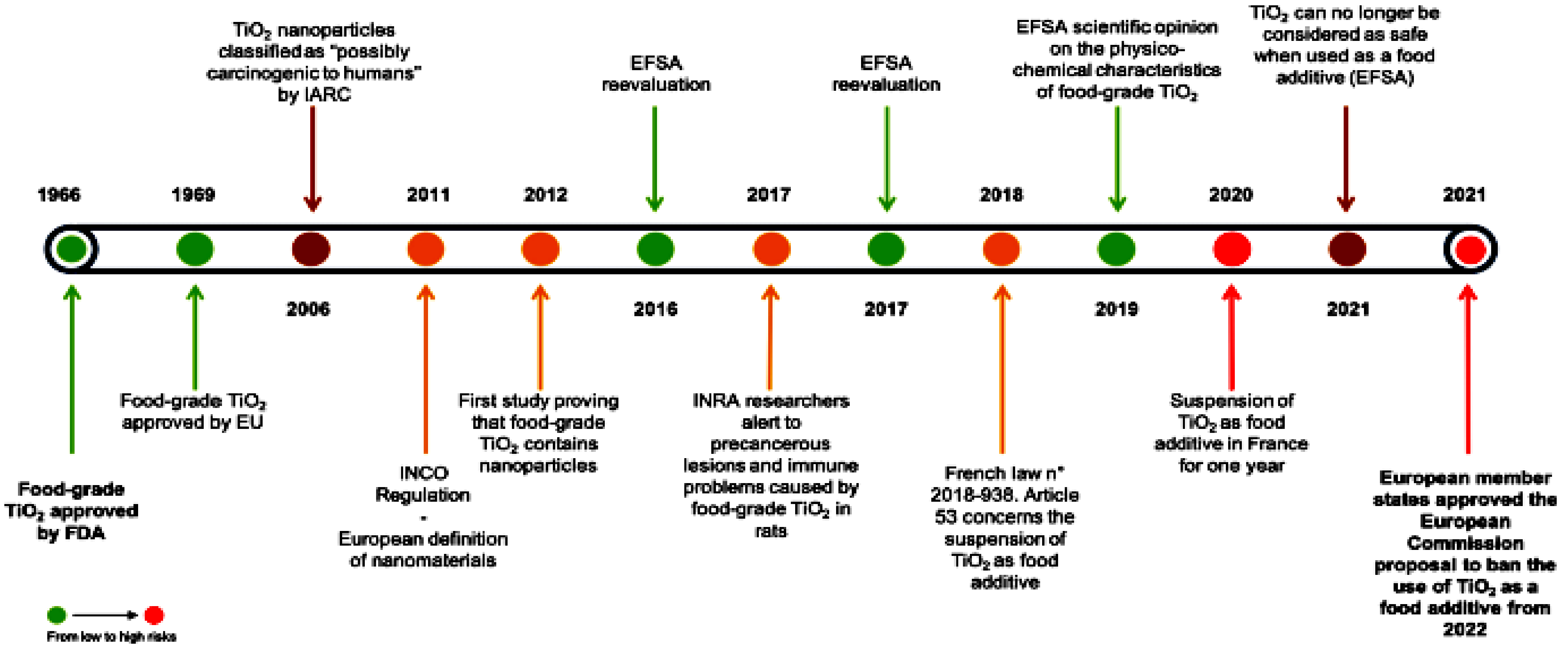
- As a color additive (E171) to make food more visually appealing
- To give colour to food that would otherwise be colourless
- To restore the original appearance of food.

SOURCES OF EXPOSURE

Unintentional Exposure

- **Food Contact Materials** – Leaching from plastics and coatings used in food packaging
- **Agricultural inputs** – Fruits, vegetables, and grains grown in contaminated soils.
- **Environmental contamination** – Crops irrigated with water exposed to industrial contamination.
- **Industrial Processing and Cross-Contamination**

Historical Use and EFSA's Assessments



Current Controversies and Health Concerns

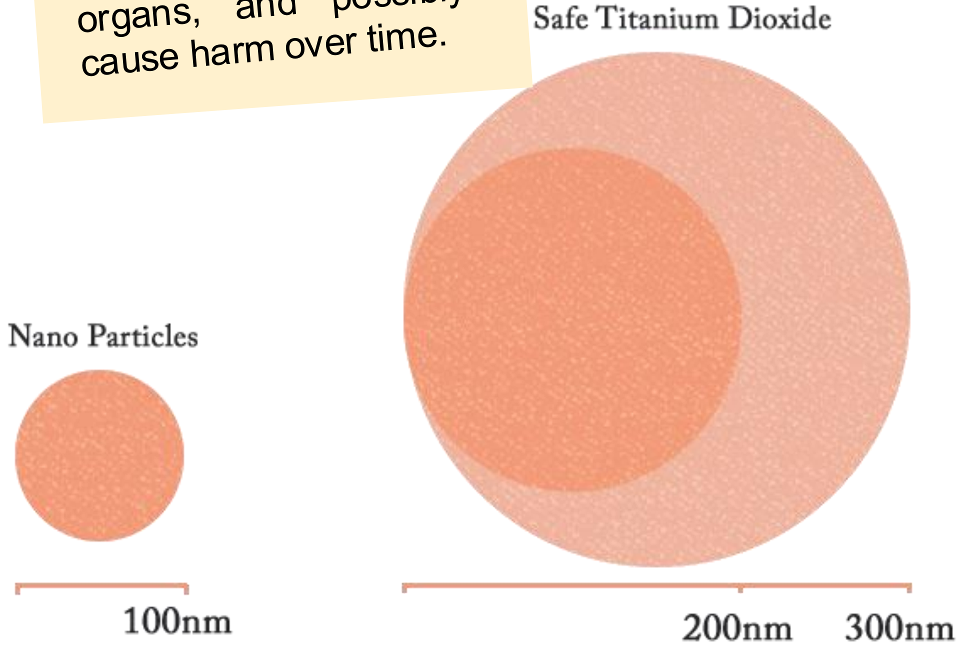
Health Risks Identified in Studies

- Possible Genotoxicity and potential DNA damage
- Possible Accumulation of nanoparticles in human tissues
- Risk to vulnerable populations (e.g., children due to high consumption of sweets)

Public and Industry Reactions

- Public concern about food safety
- Industry concerns about alternatives and production costs

With nanoparticles being **smaller than 100 nm**, there is concern that they can penetrate human tissues, accumulate in organs, and possibly cause harm over time.



Aspect	(He L. and al., 2022)	(Weir. A. and al., 2012)	(Bachler G. and al., 2015)	(Rompelberg, C., and al., 2016)	(Athinarayanan, J. and al., 2015)	(Peters, R. J. B. and al., 2014)
Study Focus	Characterization of TiO_2 nanoparticles in food products in China and estimation of dietary exposure.	Investigation of TiO_2 nanoparticles in food and personal care products in the U.S.	Dietary exposure to TiO_2 nanoparticles in Europe using a lifetime exposure model.	Dietary exposure to TiO_2 and TiO_2 NPs in the Dutch population.	Analysis of TiO_2 nanoparticles in food products and their potential toxicity in humans.	Investigation of 7 food-grade TiO_2 materials (E171), 24 food products, and 3 personal care products for TiO_2 content and particle size.
Food Products Studied	15 Chinese food products, including beverages, fig preserves, jellies, chewing gum, and confectionery.	89 food products, including candies, chewing gum, and other consumer products containing TiO_2.	Focused on lifetime dietary exposure, not specific to individual food products.	Evaluated a range of food products, including sauces, dressings, and confectionery items.	Food products, mainly confectionery and dairy items.	24 food products, including sauces, baked goods, dairy products, and 3 personal care products.

TiO_2 Nanoparticle Studies : State of the Art

Aspect	(He L. and al., 2022)	(Weir. A. and al., 2012)	(Bachler G. and al., 2015)	(Rompelberg, C., and al., 2016)	(Athinarayanan, J. and al., 2015)	(Peters, R. J. B. and al., 2014)
Mean Particle Size	53.5 to 230.3 nm, average 116.2 nm. Approximately 34.7% of the particles were smaller than 100 nm.	TiO_2 particle size ranged from 40 to 300 nm, with 36% of the particles being nanoparticles.	TiO_2 particles smaller than 100 nm were estimated to be a significant fraction of overall intake.	The proportion of nanoparticles (<100 nm) was significant but varied depending on food type.	10–36% of TiO_2 particles in food-grade additives were nanoparticles.	TiO_2 particle sizes ranged from 60 to 300 nm. Depending on the method, 10-15% of particles were below 100 nm.
Nanoparticle Fraction	34.7% of TiO_2 particles in food additives, 55.6% in chewing gum smaller than 100 nm.	36% of the TiO_2 particles in food products were nanoparticles smaller than 100 nm.	No exact fraction reported, but nanoparticle exposure was considered significant over a lifetime.	17-35% of TiO_2 particles in Dutch food products were nanoparticles.	10–36% of TiO_2 particles in food-grade additives were nanoparticles.	5-10% of TiO_2 particles in food and personal care products had sizes below 100 nm.
TiO_2 Content in Food	3.2 to 3409.3 µg/g, with chewing gum having the highest concentrations.	TiO_2 content in U.S. food products (candy, gum) averaged around 1500 µg/g, with some products at 3000 µg/g.	Not directly reported; focused on overall exposure estimates.	TiO_2 concentrations in Dutch food products ranged from 1 to 4000 µg/g.	TiO_2 content was similar to that found in other studies, ranging from 1 to 4000 µg/g.	Detectable TiO_2 amounts in 24 of the 27 products, ranging from 0.02 to 9.0 mg TiO_2/g product.

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Dietary Exposure	Estimated daily intake of TiO_2: 71.31 µg/kg body weight/day. NP intake: 7.75 µg/kg body weight/day.	Estimated daily intake of TiO_2 in the U.S.: 60 µg/kg body weight/day.	Lifetime exposure to TiO_2 NPs was significant for European consumers.	Dutch dietary intake of TiO_2 NPs ranged from 20 to 80 µg/kg body weight/day.	Reported similar levels of exposure, though focused on potential toxicity rather than exposure amounts.	Estimated exposure to TiO_2 based on particle size distributions in food and personal care products.
Key Findings	High TiO_2 exposure in children, raising concerns about long-term health impacts due to nanoparticle ingestion.	Significant nanoparticle presence in food, raising concerns about long-term exposure, especially for children.	Lifetime exposure was substantial, with concerns about nanoparticle accumulation in the human body.	Dutch population at risk of substantial TiO_2 nanoparticle exposure, leading to health concerns.	Significant levels of TiO_2 nanoparticles in food, raising concerns about potential health impacts.	All methods used found comparable size distributions for TiO_2 particles, with 10-15% being nanoparticles in food-grade E171.
Health Implications	Emphasized the need for stricter regulation and further risk assessment of TiO_2 NPs in Chinese food.	Called for more research into the health effects of TiO_2 nanoparticles, especially for children.	Highlighted the long-term risk of TiO_2 nanoparticle accumulation, with potential genotoxicity concerns.	Need for better regulation and monitoring of TiO_2 NPs in food due to potential health risks.	Raised concerns about the accumulation and potential toxicity of TiO_2 nanoparticles in human tissues.	Raised concerns about the inability of current methods to fully detect nanoparticles below 20 nm.

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TiO_2 Nanoparticle Studies : State of the Art

PARTICLE SIZE OF E171

Food-grade titanium dioxide particles typically range from 200 to 300 nm

GLOBAL PRESENCE OF TiO_2

TiO_2 content varied widely, from around 1 to over 4000 μg/g in all regions

PARTICLE SIZES IN FOOD PRODUCTS

TiO_2 Particle sizes range from 40 to 300 nm across studies

PRESENCE OF NANOPARTICLES

Generally 10-36% of E171 particles are smaller than 100 nm particles

Comparative Assessment of Unintentional Exposure to (TiO_2)

Aspect	Packaging Materials (Yang, Y. and al., 2015)	Agricultural Inputs (Keller, A. A. and al., 2013)	Environmental Contamination (Gottschalk, F., and al., 2011)
Exposure Source	Leaching from food packaging materials, especially plastics and coatings	Use of TiO_2 in pesticides, fertilizers, and soil amendments	Industrial runoff contaminating water supplies, which are used for irrigation
Exposure Pathway	Direct contact between food and packaging materials	Crops absorbing TiO_2 nanoparticles from soil and water	Crops absorbing TiO_2 through contaminated irrigation water
Food Types Affected	Acidic and high-fat foods, due to increased interaction with packaging	Fruits, vegetables, and grains grown in contaminated soil	Crops grown in areas exposed to industrial water contamination
TiO_2 Exposure Level (mg/kg)	Up to 0.1 mg/kg (depending on packaging, food acidity, and storage conditions)	0.05 to 0.5 mg/kg (in plant tissues depending on exposure and accumulation)	0.01 to 0.1 mg/kg (based on water and soil contamination levels)
Potential Risk Factors	Heat, long-term storage, and acidic foods increase nanoparticle migration	Potential bioaccumulation over time and across seasons	Proximity to industrial activities and long-term water contamination
Regulatory Oversight	Limited focus on nanoparticle leaching from packaging materials	Limited, especially regarding long-term nanoparticle accumulation in crops	Environmental regulation of industrial runoff but limited focus on nanoparticle effects
Key Findings	Leaching is dependent on material composition and food characteristics	Accumulation in plant tissues varies based on exposure but can persist	Long-term contamination of water supplies can lead to gradual TiO_2 buildup in crops

TiO_2 contamination levels in food can range from **0.01 to 1 mg/kg due to environmental contamination** or leaching from packaging.

Comparison of Regulatory Frameworks

Assessment Criteria	JECFA	EFSA	Comparison and Opinion of Other Risk Assessment Agencies
ADI (mg/kg bw per day)	Not specified. JECFA reaffirmed the ADI as "not specified," indicating no health risks at typical exposure levels	EFSA Can no longer establish ADI due to concerns about genotoxicity	EFSA outlier internationally – Health Canada; US FDA; FSANZ, Japan Food Safety Commission disagree with EFSA Assessment and align with JECFA
Relevant Studies	JECFA's 97th meeting reviewed toxicokinetics, acute, short-term, and long-term toxicity, carcinogenicity, genotoxicity, and reproductive/developmental toxicity. No significant health risks were observed. Available data did not provide convincing evidence of genotoxicity for INS 171	EFSA's 2021 re-evaluation identified concerns about the genotoxic potential of nanoparticles smaller than 100 nm in E171. EFSA focused on uncertainties related to long-term exposure and the potential accumulation of nanoparticles	EFSA placed more emphasis on nanoparticle risks with studies where TiO2 nanoparticule proportion is not representative of FoodGrade TiO2
ARfD (mg/kg bw)	Not required due to low bioavailability and no identified short-term risks	No ARfD established	Not relevant for EFSA given the concerns expressed; All other agencies concurwith JECFA
Relevant Effect	JECFA noted no significant toxicological effects from oral exposure, including no carcinogenicity or reproductive/developmental toxicity. INS 171 was not carcinogenic in 2-year studies at doses up to 7,500 mg/kg bw per day in mice and 2,500 mg/kg bw per day in rats. Available studies also showed no reproductive toxicity at doses of up to 1,000 mg/kg bw per day	EFSA highlighted potential DNA damage from nanoparticle exposure, focusing on unresolved uncertainties regarding genotoxicity. These concerns led to a precautionary ban	JECFA found no carcinogenic or reproductive risks, while EFSA emphasized genotoxicity concerns, as a result of the the consideration of a nanoparticule proportions not representative of Food Grade Applications. Other agencies concur with JECFA
Dietary Exposure	JECFA assessed dietary exposure based on mean use levels in 11 food categories. For example, in Europe, P95 exposure estimates for toddlers (1–2 years) could reach 28 mg/kg bw per day. However, JECFA reaffirmed its ADI "not specified" based on the low oral absorption and absence of any identifiable hazard leading to possible use at GMP	EFSA recommended banning E171 due to potential long-term health risks, particularly related to DNA damage from nanoparticles	JECFA selected a high estimate of 10 mg/kg bw per day for dietary exposure to INS 171, focusing on low absorption and lack of identifiable hazards.

Regulatory Positions on Titanium Dioxide (E171)

EUROPEAN FOOD SAFETY AUTHORITY

Declared E171 **unsafe** as a food additive due to concerns over potential DNA damage and genotoxicity, leading to a ban in the EU.

JECFA JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES

CODEX ALIMENTARIUS International Food Standards

Maintained **approval** of E171, calling for more research, with no immediate ban implemented.

Countries Relying on EFSA Assessment

TiO2 banned as a food additive

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1. Identify Safe (and equally well studied) Alternatives to TiO_2 as a Whitening Agent ensuring they offer similar functionality without the associated health risks.

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2. Develop Regulatory Cut-Off levels for Compliance verification

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3. Differentiate between intentional food additive use and unintentional environmental presence.

Food Additive Use Banned	versus	Environmental Presence possible at various levels

Pilot study : Establishment of cut-off Level

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DEVELOPMENT OF A PRACTICAL COMPLIANCE VERIFICATION APPROACH

Distinguishing Levels of Titanium Dioxide used as a Food Additive

Descriptive statistics on TiO_2 concentrations (ppm) used intentionally in food samples (n = 403).

Min	25th percentile	Median	75th percentile	Max	Mean	Standard deviation
0.046	5.020	300.6	1412.0	19130.0	1207.9	2150.9

Descriptive statistics of TiO_2 concentrations (ppm) of the data set without upper outliers (n = 290).

Min	25th percentile	Median	75th percentile	Max	Mean	Standard Deviation
0.015	0.36	0.87	2.72	30.0	3.0	5.22

Descriptive statistics of TiO2 concentrations (ppm) of the data set after removal of outliers and skewness adjustment (n = 272).

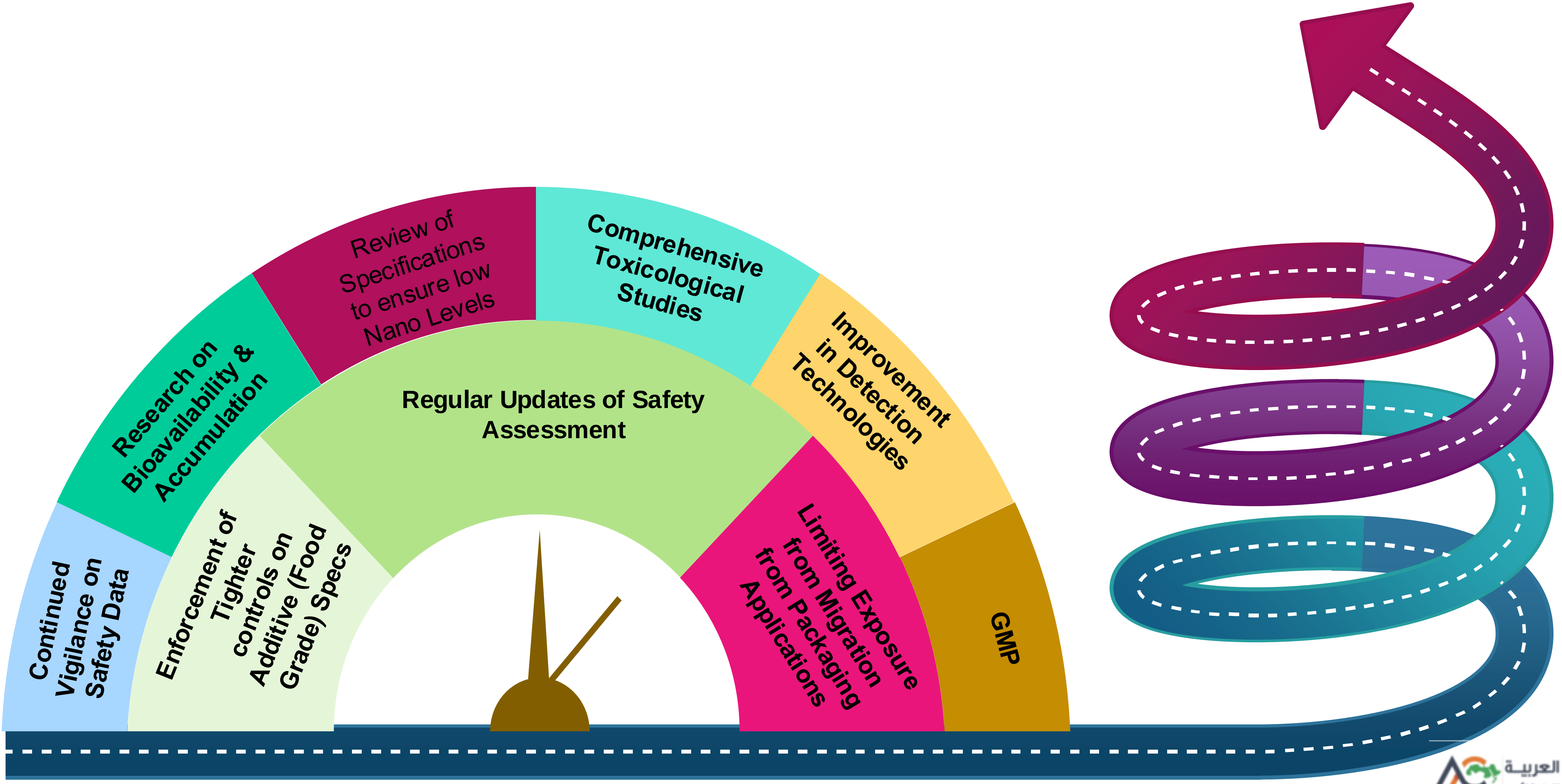
Min	25th percentile	Median	75th percentile	Max	Mean	Standard deviation
0.085	0.43	0.9	2.76	23.4	2.84	4.55

Levels below 25 ppm would **rule out intentional addition** of TiO_2 as a food additive.

Recommended Cut-Off Threshold: 25 ppm (mg/kg).

Levels Exceeding 25 ppm: Would **initiate an investigation** to determine if TiO_2 was used intentionally..

Countries that Concur with JECFA/Codex Direction



Conclusion

The results of studies showing concers were obtained with materiel that does not represent Food Grade Application


thank you
danke
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Баярлалаа
спасибо
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