

PQRI Workshop:
TiO₂ Use in Pharmaceuticals
Global Regulatory and Technical Challenges

June 13-14, 2023

SUMMARY OF DAY 1 BREAKOUTS



Product Quality Research Institute

PQRI Workshop:
TiO₂ Use in Pharmaceuticals
Global Regulatory and Technical Challenges

Breakout Session 1: June 13, 2023

BREAKOUT ROOM #1

Scientific Understanding & Awareness of the Safety of TiO₂

Moderators:

Uma Bruen

Notetakers:

Kevin Hughes



Product Quality Research Institute

TiO₂ History of safe use (Group 1: toxicologists, safety experts)

1. Hazard is not Risk: Should the assessment EU conducted (which is different from rest of the world) have been based on real risk versus hazard potential?
 - How many Skittles do you need to eat for there to be a safety concern? An adult would have to eat 4,080 skittles – each and every day – for over 9 years – to achieve the genotoxic dose in someone's spleen,
 - How many TiO₂-coated tablets do you need to take for there to be a safety concern? Estimated 681 tablets per 6 hrs to achieve some measure of toxicity
2. Should a Maximum daily exposure level be assigned to TiO₂, and how should this be done?
 - How do arrive at an ADI? What data/study could be used, exposure duration, route of exposure, etc.?
 - Can we ask industry to provide this?
3. Do you agree with EFSA that a concern for genotoxicity cannot be excluded, or with the expert panel that there is no evidence of direct genotoxic activity, or are you unable to reach a conclusion and believe more data is needed?
4. If you believe more data is needed, what do you think of the new genotoxicity studies proposed by TDMA?
5. The NTP performed a GLP 2- year bioassay in rats and mice involving administration of a TiO₂ similar to E171 up to 5% of the diet without any evidence of carcinogenicity or preneoplastic changes, including in the colon. Should this be considered adequate demonstration of its lack of carcinogenic activity?



Question 1

- Hazard is not Risk: Should the assessment EU conducted (which is different from rest of the world) have been based on real risk versus hazard potential?
 - How many Skittles do you need to eat for there to be a safety concern? An adult would have to eat 4,080 skittles – each and every day – for over 9 years – to achieve the genotoxic dose in someone's spleen,
 - How many TiO₂-coated tablets do you need to take for there to be a safety concern? Estimated 681 tablets per 6 hrs to achieve some measure of toxicity

Real Risk 10

Hazard Potential 0



Question 2

- Should a Maximum daily exposure level be assigned to TiO₂, and how should this be done?
 - How do arrive at an ADI? What data/study could be used, exposure duration, route of exposure, etc.?
 - Can we ask industry to provide this?

Max Daily Exposure/ADI for TiO₂

Yes 10

No 0

Who sets it?

- Depends – NTP/NIH study says there is no carcinogenicity
- TDMA Proposed 1000mg/kg body weight per day as a starting point.
- FDA limit is 1% by weight in foods, this may change based on the new science programme.
- Wait for JECFA outcome, they should come up with an ADI



Question 3 & 4

- Do you agree with EFSA that a concern for genotoxicity cannot be excluded, or with the expert panel that there is no evidence of direct genotoxic activity, or are you unable to reach a conclusion and believe more data is needed?
 - Agree with EFSA Opinion 0
 - Expert Panel 7
 - More Data 1
- Any RA assessment is conducted based on the papers available at the time, should there be a consistent /constant review process to review updated data. Is there a way to get EFSA to take another look at the data and reconsider the outcome even in foods.
- Would need the commission to mandate EFSA to do this, but even if this is managed and a positive Opinion is achieved it would still have to get through the Commission and parliament and this would stop any change dead.
- Expend the resources on preserving pharma use, EMA make the final decision with the new Pharma Regs Draft.
- Patient Advocacy groups to lobby parliament, or at least to raise the volume.



Question 5

- The NTP performed a GLP 2- year bioassay in rats and mice involving administration of a TiO₂ similar to E171 up to 5% of the diet without any evidence of carcinogenicity or preneoplastic changes, including in the colon. Should this be considered adequate demonstration of its lack of carcinogenic activity?
- Yes, but hard to predict what the assessor will decide. Will they always raise an issue no matter what you do?

PQRI Workshop:
TiO₂ Use in Pharmaceuticals
Global Regulatory and Technical Challenges

Breakout Session 1: June 13, 2023

BREAKOUT ROOM #2

Scientific Understanding & Awareness of the Safety of TiO₂

Moderators:

George Collins

Notetakers:

Courtney Callis



Public Education/Perception of TiO₂ safety (Group 2 : Safety, marketing, communication professional)

- 1 . What type of communication tools should be created to provide more understanding of the safety of TiO₂? Especially to public understanding/awareness?
 - FAQ on TiO₂, consumer knowledge, perception,
 - Example: TiO₂ exposure thru food, maybe estimate number of Skittles you need to eat to be safety concern (e.g. 4080 per day for 9 years)
 - How many TiO₂-coated tablets do you need to take for there to be a safety concern? Estimated 681 tablets per 6 hrs to achieve some measure of toxicity
- 2 . How do we effectively communicate/educate the “safety of TiO₂” to consumers, public, politicians?
 - You tube video? Programs, factsheets? Graphical presentation/Imaging on Safety of TiO₂
 - How do we get this messaging thru to public in format that is understood?
- 3 . In Dr Cohen’s talk, Weight of evidence presented indicates E171 has none of the properties for it to be human carcinogen. What may be simple way to help public understand “weight of evidence” concept for help the understand “TiO₂ history of safe use”?
4. With the presentations given today, do you believe TiO₂ should be banned as a food additive?
 - a. Full ban: no TiO₂ in the formulation
 - b. Limited
 - c. Nanoparticles TiO₂
5. Should Politics override the science?



Notes – Question 1

1 . What type of communication tools should be created to provide more understanding of the safety of TiO₂? Especially to public understanding/awareness?

FAQ on TiO₂, consumer knowledge, perception,

Example: TiO₂ exposure thru food, maybe estimate number of Skittles you need to eat to be safety concern (e.g. 4080 per day for 9 years) ; How many TiO₂-coated tablets do you need to take for there to be a safety concern? Estimated 681 tablets per 6 hrs to achieve some measure of toxicity

Skittles is simplest visual (film coating manufacturer); could also use Tylenol but that is a “more dangerous” communication because if we use it, we underscore there is an issue

- Start with how people are getting information (they’re getting news of lawsuits from social media)

Equally important, clarify the word “titanium” to move away from impression of “pieces of metal” vs an element

- Tell a story and show where Ti comes from; comes from earth; processing steps cartoon?
- Typical applications

Alternative: “Appeal to fears” and weigh benefit risk calculus (access to medicines needed to stay healthy would decline)?

- Downside: in the context of pharmaceuticals, this would come off as greedy
- Instead: show TiO₂ is everywhere and has been safe for decades
- Picture of supermarket wall showing all products with TiO₂ next to pic with all those that would go away
- Picture of pharmacy with the same

How many people have died from TiO₂?



Notes Question 2

2 . How do we effectively communicate/educate the “safety of TiO₂” to consumers, public, politicians?

-How to reach out beyond ourselves?

You tube video? Programs, factsheets? Graphical presentation/Imaging on Safety of TiO₂

How do we get this messaging thru to public in format that is understood?

-Social Media (TikTok, Instagram)

Hire a media organization or PR company for a video or news segment

Many feel news segment isn't the best avenue, more entertainment (like the Simpsons?) or social media would be better

Need perception of independence

-NOT newspaper, nightly news, or peer reviewed journal. Has to be social media or picked up by news feeds/social media

-Capture disinformation as part of the equation; clarify where misinformation is coming from and turn around to educate

-Schools with science programs (outreach) on food safety (is “food safety day” a thing in the US??)

-School science days/local level; documentary?

-Multipronged approach (many means, venues)

-60 Minutes type is big enough if it comes up on all the news channels

-Align with energy of the state legislations (are we too late?)

-Consider multi languages

(how to try to put out fire in France? If we don't put it out there, we won't be able to?)

-Story book of safety; message that is short and clear

-Catchy title to invite people to read or listen



Notes Question 3

3 . In Dr Cohen’s talk, Weight of evidence presented indicates E171 has none of the properties for it to be human carcinogen. What may be simple way to help public understand “weight of evidence” concept for help them understand “TiO2 history of safe use”?

How we share our knowledge is equal to the knowledge we share!

Public would not understand WOE, it is too deep, too technical for them; needs to be simple otherwise it gets too scary for them.

Target trade organizations of doctors, nurses, pharmacists, hospitals as care givers for messaging? (Non-manufacturer, non-pharma has more credibility/trust)

- Other consortia (Europe: FIP? APB?; US: AAPS, state-level like hospital pharmacists for the State of New York) to educate doctors in Europe, WHO
- Train and educate these care givers/health practitioners
- Trickle down the information
- Doctor’s office sign that says “Ask me about titanium dioxide”

If patients learn medicine being promoted via media could be banned (not be available), that will get their attention

Students’ science fair project? Contact toxicology education foundation?

Don’t connect to paint because people will jump to lead

Patient advocacy groups who worry about access and cost of healthcare could be allies;

WHO ally

Physician groups ally

Learn lessons from Europe: ask food industry there to ask what they would have done to avoid this issue? What kind of educating/lobbying did they do or not do?



Notes Question 4 & 5

4. With the presentations given today, do you believe TiO₂ should be banned as a food additive?

- a. Full ban: no TiO₂ in the formulation**
- b. Limited**
- c. Nanoparticles TiO₂**

Compelling data is not currently sufficient for ban.

5. Should Politics override the science?

No. Ask instead, “How do you prevent the politics from overriding the science?”

Follow the money or power (name recognition for making national news is a personal promotion tactic for a politician)

IF public health authorities are backing a ban, then politicians will win every time. We have to create faith in government.

- FDA is not backing the ban
- The big money is coming from those who are sowing lack of trust in the government
- How to dispel the myths of the day (come factor is fear, control, click bait, sensational news)
- How do we connect with politicians?
 - IPQ Journal is national/international
 - Communication or marketing to state politicians is tricky

