Gestion du risque associé aux nanoparticules de TiO2 à Sanofi

Marion Boyer – 31/05/2018

Pourquoi s'y intéresser ?

« potentiel cancérogène »
60 millions mag (2018)

« EU member states support change to titanium dioxide classification »
Chemical Watch (2018)

« Inhaling nano-titanium dioxide could have epigenetic effects in foetus »
Chemical Watch (2018)

« Dioxyde de titane nanométrique : de la nécessité de proposer une valeur d'exposition professionnelle »
INRS (2016)

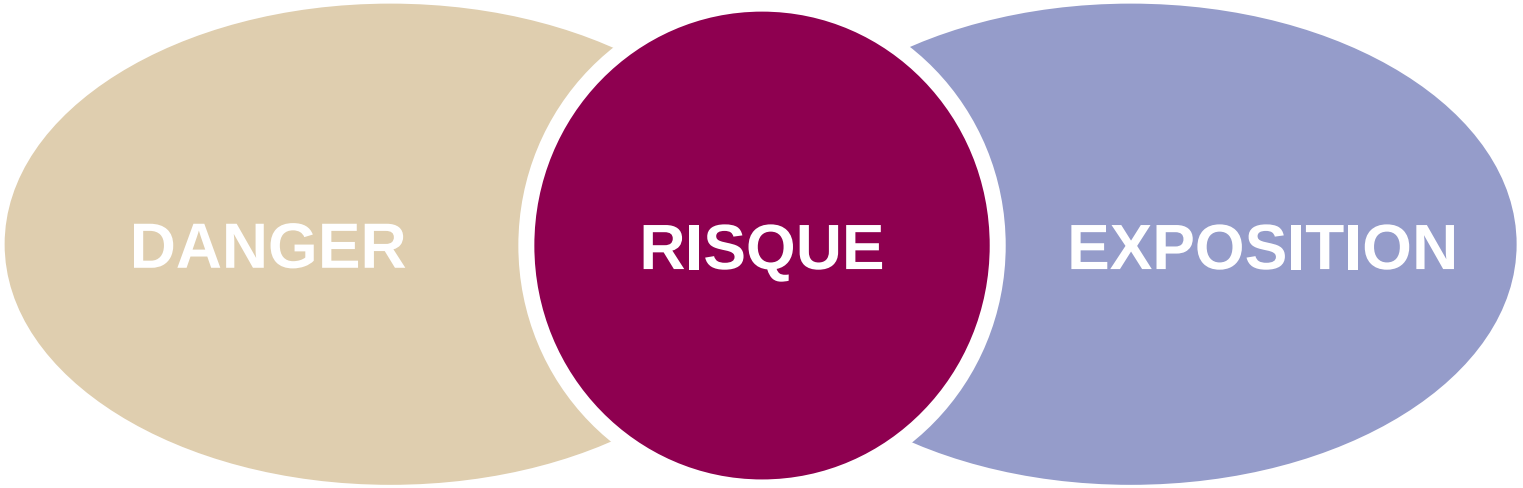
« can cause birth defects »
The Times of India (2018)

« NIOSH Sets Recommended Exposure Limits For Titanium Dioxide, Including Nanoparticles »
Bloomberg BNA (2011)

« When nanotech turns nanotoxic »
CBS news (2014)

Comment gérer le risque ?

Avec une démarche habituelle



Identifier la toxicité

Définition de la substance
Voies d'exposition
Données de toxicité

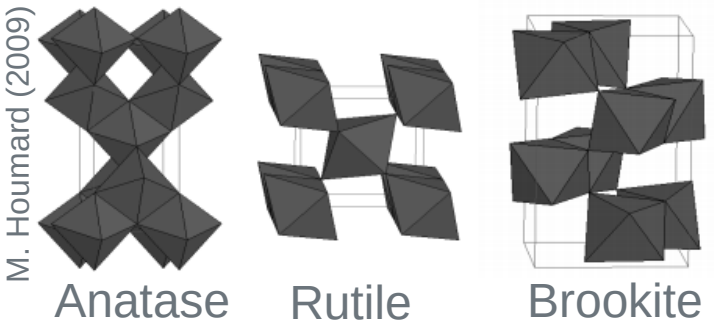
Evaluer l'exposition

Qui ? (potentiellement)
Comment ? (process)
Quelles protections ?
Métrologie

Quelles difficultés ? (1/2)

DANGER

Caractéristiques physico-chimiques



→ Taille, forme, structure cristalline… influencent la toxicité

Granulométrie

- En masse/volume : ***d50 ~ 120-150 nm***
- En nombre : ***d50 ~ 60 nm***

→ Importance de l'unité de mesure

Voie d'exposition – exemple voie cutanée

Pas de toxicité… sur **peau saine** → Relativiser données

Quelles difficultés ? (2/2)

EXPOSITION

Cadre règlementaire limité

- Déclaration
  R-nano (France) ; ~~REACH~~
- Etiquetage (selon industrie)
  Pharmaceutique hors scope

→ Pas de VLEP règlementaire

Mesures de protection

- Efficacité ?
- Qui protéger ?
  Opérateurs, maintenance…

→ Mesures actuelles adaptées ?

Quelles solutions ? (1/3)

DANGER – TiO2 nano

Données d'institutions

CIRC	INRS	ANSM	Stoffenmanager nano
TiO2	*Tous nano*	*TiO2 & ZnO*	*TiO2*
cancérogène 2B par inhalation	Toxicité non spécifique, indirecte…	Pas de passage cutané sur peau saine	Hazard class: « very high »

! Données parfois anciennes

Revue de littérature

- **Voie respiratoire :**
  Toxicité Poumons + Système nerveux central + Foie
- **Voie cutanée :**
  Considérer passage

Quelles solutions ? (2/3)

EXPOSITION

VLEP – Recommandations du NIOSH

Poussières non spécifiques (France)	*Particules fines TiO2* (NIOSH)	*Forme nano TiO2* (NIOSH)
10 mg/m3	**2,4 mg/m3**	**0,3 mg/m3**

Mesures de protection – Recommandations du NIOSH

“Workplace design solution” (03/2018)

- “Protecting Workers during **Intermediate and Downstream Processing** of Nanomaterials”
- “Protecting Workers during the **Handling** of Nanomaterials”
- “Protecting Workers during Nanomaterial **Reactor Operations**”

NTRC NANOTECHNOLOGY RESEARCH CENTER

Controlling Health Hazards When Working with Nanomaterials: Questions to Ask Before You Start

Here are some questions you should ask yourself before starting work with nanomaterials.

Here are some options you can use to reduce exposures to nanomaterials in the workplace. These options correspond with the questions on the left.

(1) FORM

Have you done a job hazard analysis? What is the physical form of the nanomaterial? How much are you using? Can you reduce exposure to the nanomaterial by changing its form (for example, putting powder into a solution) or reducing the amount you are using?

DRY POWDER
(typically highest potential for exposure)

SUSPENDED IN LIQUID

PHYSICALLY BOUND/ ENCAPSULATED
(typically lowest potential for exposure)

(2) WORK ACTIVITY

How are you using the nanomaterial? Could the work activity cause exposure? Is the likelihood of exposure low or high? Can you change the way you do the activity to reduce the exposure?

Applies to Dry Powder Nanomaterials
- Higher potential for exposure: Dumping bags of powder, bagging or sieving of products
- Lower potential for exposure: Scooping/weighing of product, transporting containers with light surface contamination or closed barrels/bottles/bags

Applies to Nanomate pended in Liquids
- Higher potential for expo praying, open top sonication, producing a r
- Lower potential for expo aning up a spill, pipetting small amounts, ng

Applies to Physically Bound/Encapsulated Nanomaterial
- Higher potential for exposure: Cutting, grinding, sanding, drilling, abrasive blasting, thermal release
- Lower potential for exposure: Manual cutting and sanding, painting with a roller or brush

(3) ENGINEERING CONTROLS

Based on the form and the work activity, what engineering controls will be effective? What are the key design and operational requirements for the control? How does the non-nanomaterial base material or liquid affect exposure?

Applies to Dry Powder Nanomaterials
- Chemical fume hood
- Ventilated baggi or
- handling enclosure
- exhaust ventilati

Applies to Nanomaterial Suspended in Liquids
- Chemical fume hood
- Glove box
- Nanomaterial handling enclosure
- Local exhaust ventilation
- Ventilated spray booth

(4) ADMINISTRATIVE CONTROLS

Have you considered the role of administrative controls? Have you set up a plan for waste management? Have you considered what to do in case of a spill or how you will maintain equipment?

- Establish a chemical hygiene plan
- Perform routine housekeeping
- Train workers
- Use signs and labels
- Restrict access to areas where nanomaterials are used

(5) PERSONAL PROTECTIVE EQUIPMENT

If the measures above do not effectively control the hazard, what personal protective equipment can be used? Have you considered personal protective equipment for the non-nanomaterial base material or liquid?

- Nitrile or chemical resistant gloves
- Lab coat or coveralls
- Safety glasses, goggles, or face shield

Applies to All Nanomaterial Forms
- Respiratory protection when indicated and engineering controls cannot control exposures, and in accordance with federal regulations (29 CFR 1910.134)
- NIOSH guidance on respirators can be found at www.cdc.gov/niosh/topics/respirators/
- Use personal protective equipment during spill cleanups and equipment maintenance

Centers for Disease Control and Prevention | National Institute for Occupational Safety and Health | NIOSH

Are you interested in learning more about how you can safely work with nanomaterials or want to stay up-to-date on nanotechnology safety? See the NIOSH NTRC website for more information and links to guidance documents: www.cdc.gov/niosh/topics/nanotech/

DHHS (NIOSH) Publication No. 2018-103 | February 2018
https://doi.org/10.26616/NIOSHPUB2018103

SANOFI

Dans la pratique (1/9)

SANOFI

Prise en main du sujet – niveau global

- **Création d'un working group**

  ! Décision du comité d'éthique

- **Impliquer tous les départements**

  Risk management, Public Affairs, Safety Science, Science Policy, R&D, Quality, HSE…

  ! Gérer le risque ensemble

Dans la pratique (2/9)

HSE

Qui / Comment ?

1

Identifier les risques

- **Recenser les sites**
  Croisement de sources (Questionnaire + Données des Achats)
- **Identifier la substance**
  Fournisseurs ?
  Part nanométrique (Granulométrie)
- **Identifier les risques**
  Nombre d'exposés
  Comment ils sont exposés/protégés

! Unité de mesure

Dans la pratique (3/9)

HSE

Questionnaire – identifier la substance

1. Are you using TiO2 **(any form)** in the facility?

○ Yes ○ No

4. Please provide the **particle-size distribution chart of TiO2** used in the facility as an attached file.

If available, please provide a number distribution. If not, provide the one available (volume/mass distribution…).

Please answer all questions below even if the chart is not indicating presence of nanosized (under 100 nm) materials.

Unité de mesure
Partir du principe qu'on ne sait pas s'il y a des nano

Dans la pratique (4/9)

HSE

Questionnaire – Identifier les travailleurs exposés

5. **How many people…**

If you have trouble answering sub question a., at least answer sub question b.

a. Are working in the facility	b. Are working with or near TiO2 *

* *"Near TiO2" refers to people working in the same area as workers who are handling TiO2 or as machines that use TiO2 (in the case of automated workflow). This includes cleaners, waste operators and maintenance.*

We are talking about TiO2 as a raw material, not about finished products having TiO2 in their composition.

Dans la pratique (5/9)

HSE

Questionnaire – Identifier les méthodes de manipulation

11. How is TiO2 used?

- ☐ TiO2 is handled by operators
- ☐ TiO2 is used inside machines

If yes:

a. **What kind** of machines?

- ☐ Open (TiO2 can come into contact with ambient air: open device or sealed device in bad condition)
- ☐ Enclosed (TiO2 can not come into contact with ambient air: sealed device in roadworthy condition)

b. **Where** are the machines?

- ☐ In the same area as workers
- ☐ In a separated area (workers only have access to the area if they purposely enter it)

10. In the facility, TiO2 is used…

- ☐ As powder
- ☐ In liquid form
- ☐ In gel form

Dans la pratique (6/9)

HSE

Questionnaire – Identifier les méthodes de maintenance

12. About the **cleaning process**:

HELP

Dry materials *refer to brooms, brushes, dry cloths…*
Wet materials *refer to wet cloths, wet wipes…*

12.2. The **equipment/machines**:

c. How often are the followings cleaned?

	Cleaning frequency	Cleaning tools
Inside the equipment/ machines	○ At least once a day ○ More than once a week ○ Once a week ○ At least once a month	☐ Dry materials ☐ Vacuum ☐ Wet materials ☐ Clean-In-Place
Outside the equipment/ machines	○ At least once a day ○ More than once a week ○ Once a week ○ At least once a month	☐ Dry materials ☐ Vacuum ☐ Wet materials

Dans la pratique (7/9)

HSE

Questionnaire – Identifier les mesures de protection

13. Currently, do the concerned workers have access to the protective equipment named below?

		Avail	N.A.	R.C.	HEPA	Rec.A
General ventilation	(Lab)	○	○	☐	☐	☐
	(Prod)	○	○	☐	☐	☐

! Bon état de marche

Please indicate the air change rate:

number of air changes per hour

! Type de filtre

What is the fresh air proportion?

- ○ 100% (only outside air, no recuperation)
- ○ 0% (only inside air, recirculation)
- ○ Mixed air:

% of fresh air

! Air recirculé

Dans la pratique (8/9)

HSE

Que faire ?

2

Gérer les risques

- **Mettre à jour le guide interne sur les nano**
  Avec données récentes
  Uniformiser les informations pour les différents sites
- **Mettre en place les mesures de protection**
  En fonction des recommandations
- ***Informer les opérateurs***
  Questionnaire : aspect pédagogique
  Communication interne

Plus de confinement

Dans la pratique (9/9)

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Avenir du sujet

3

Suivi

- **Traçabilité des informations**
- **Veille scientifique & règlementaire**

Décisions politiques

« Le gouvernement prévoit de **suspendre** « **avant la fin de l'année** » l'utilisation des nanoparticules de **dioxyde de titane comme additif alimentaire** en France », Le Monde (17 mai 2018).

- **Workshop nanomatériaux Sanofi**

Idées de sources à consulter (1/2)

Informations sur la toxicité

INRS	http://www.inrs.fr/risques/nanomateriaux/effets-sante.html
Cancer-environnement	http://www.cancer-environnement.fr/402-Nanomateriaux.ce.aspx
Anses	https://www.anses.fr/fr
PubMed	https://www.ncbi.nlm.nih.gov/pubmed/
Scopus	https://www.scopus.com/

Veille règlementaire

REACH	https://reach-info.ineris.fr/focus/reach-et-les-nanomat%C3%A9riaux
INERIS	https://www.ineris.fr/fr/recherche-appui/focus/nanomateriaux/bulletin-de-veille-thematique-nanomateriaux

Idées de sources à consulter (2/2)

Aides à la prévention des risques

INRS	http://www.inrs.fr/risques/nanomateriaux/prevention-risques.html
NIOSH	https://www.cdc.gov/niosh/updates/upd-03-12-18.html
ANSM	http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Nanoparticules-de-dioxyde-de-titane-et-d-oxyde-de-zinc-dans-les-produits-cosmetiques-Etat-des-connaissances-sur-la-penetration-cutanee-genotoxicite-et-cancerogenese-Point-d-information
Stoffen manager nano	https://nano.stoffenmanager.nl/

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