5. KONGRES SLOVENSKEGA TOKSIKOLOŠKEGA DRUŠTVA

MIKRO- IN NANODELCI- TVEGANJA UPORABE IN IZPOSTAVLJENOSTI

MICRO- AND NANOPARTICLES- RISKS OF USE AND EXPOSURE

Ljubljana, 17.6.2021

Univerza v Ljubljani Biotehniška fakulteta

Univerza v Ljubljani Fakulteta za farmacijo

univerzitetni klinični center ljubljana
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SPREMNA BESEDA

Spoštovani udeleženci 5. kongresa Slovenskega toksikološkega društva!

V preteklem desetletju smo se tudi v Sloveniji začeli zavedati pomena določanja in raziskav o vplivu delcev različnih velikosti na okolje in človeka ter s tem razvijati področje kemijske varnosti tako na strokovni kot upravni ravni. Pri tem sodelujejo mnogi strokovnjaki, med katerimi je veliko število članov Slovenskega toksikološkega društva, zato je odločitev, da se izbere to temo za 5. kongres našega stanovskega združenja, razumljiva. Še posebno, ker je to področje trenutno eno najbolj "vročih" tako v raziskovalnem kot tudi regulatornem podgledu.

Tako bo v prvi sekciji Mikro- in nanodelci ter biološki sistemi predstavljen pregled obstoječih nanomedicinskih aplikacij ter raziskav s tega področja v Evropi. Prikazani bodo tudi rezultati projektov H2020, ki se ukvarjajo z upravljanjem tveganj, povezanih z nanomateriali. Na področju varne uporabe nanodelcev bo predstavljen primer uporabe nanodelcev titanovega dioksida in cinkovega oksida v kozmetični industriji. Sekcijo pa bo zaključilo predavanje o lipoproteinskih koloidih s prehodno identiteto in stabilnih nanosomih.

V nadaljevanju bodo predstavljeni toksični učinki mikro- in nanodelcev na človeški organizem in posledično na zdravje človeka. Sledil bo prikaz upravljanja obstoječih podatkov o nanovarnosti ter različnih metod za detekcijo in lokalizacijo nanomaterialov v rastlinskih in živalskih tkivih ter uporabnost različnih nanomaterialov v naprednih oksidativnih metodah za odstarnjevanje onesnažil v odpadnih vodah.

V zadnjem delu kongresa želimo predstaviti zakonodajne aspekte izpostavljenosti nanomaterialom skozi Uredbo REACH in Uredbo o kozmetičnih izdelkih, pa tudi nedavne spremembe in razmisleke o trenutnih izzivih izvajanja določb zakonodaje in povezanih dejavnosti. Orisane bodo posebnosti ocene tveganja za zdravje ljudi zaradi izpostavljenosti nanodelcem iz okolja, s primerom ocene tveganja zaradi izpostavljenosti nanodelcem iz materialov v stiku z živili, in izzivi pri pridobivanju informacij iz recenziranih znanstvenih člankov, ki se uporabljajo za oceno tveganja. Prikazana bo analiza in vključitev dokazov iz ustreznih in zanesljivih študij pri oceni varnosti aditiva za živila titanovega dioksida ter osvetljeni različni izzivi pri študijah njegove oralne toksičnosti.

Upamo, da se bo za vsakega izmed udeležencev v programu tega kongresa našla tematika, ki ga bo še posebej pritegnila, morda se z njo tudi sam raziskovalno ukvarja. Želimo, da se znanja s tega področja povezujejo in dograjujejo tudi v slovenskem strokovnem in znanstvenem prostoru.

Marija Sollner Dolenc
Metoda Dodič Fikfak
Alenka Franko
Viviana Golja
Sara Novak

KAZALO VSEBINE

PROGRAM

8.30 - 9.00	Registracija
9.00 - 9.10	Pozdrav udeležencem in uvodni nagovor
Mikro- in nanodelci ter biološki sistemi I Moderatorka: Damjana Drobne	
9.10-9.30	Nanomaterials in biomedical application *Nils Bohme, DECHEMA*
9.30-9.50	Nano risk governance: state of the art *Damjana Drobne, Univerza v Ljubljani, Biotehniška fakulteta*
9.50-10.10	Varnost nanodelcev anorganskih UV filtrov v kozmetičnih izdelkih *Petra Kocbek, Univerza v Ljubljani, Fakulteta za farmacijo*
10.10-10.30	Nanodelci, ki jih odpuščajo celice v svojo okolico: lipoproteinski koloidi s prehodno identiteto (mikrovezikli) in stabilni nanosomi (eksosomi) *Veronika Kralj Iglič, Univerza v Ljubljani, Zdravstvena fakulteta*
10.30 -10.50	Odmor
Mikro- in nanodelci ter biološki sistemi II Moderatorki: Metoda Dodič Fikfak/Alenka Franko	
10.30-11.20	Inhalational exposure to nanoparticles in workers monitored using oxidative stress markers *Daniela Pelclova, Charles University and General University Hospital in Prague*
11.20-11.40	Epidemiološka dognanja o vplivu nano in mikro delcev na zdravje ljudi *Metoda Dodič Fikfak, Klinični inštitut za medicino dela, prometa in športa, UKC Ljubljana*
12.00-12.20	Toksični učinki nano- in mikrodelcev *Alenka Franko, Klinični inštitut za medicino dela, prometa in športa, UKC Ljubljana*
12.20-12.40	Nano- in mikroplastika v tleh: raziskave v okviru projekta EU Horizon 2020 Papillons *Anita Kokalj Jemec, Univerza v Ljubljani, Biotehniška fakulteta*
12.40-13.00	Odstranjevanje monomerov plastike iz okolja z naprednimi oksidativnimi metodami *Gregor Žerjav, Kemijski inštitut*
13.00-13.30	Odmor
Metode za vrednotenje nanodelcev Moderatorka: Sara Novak	
13.30-14.00	Nanomaterials data management: recent advances *Thomas Exner, Seven Past Nine (7P9)*
14.00-14.20	Metode za detekcijo nanomaterialov v tkivih *Katarina Vogel Mikuš, Univerza v Ljubljani, Biotehniška fakulteta*
14.20-14.40	Uporaba vrstične elektronske mikroskopije za raziskave bio-nano interakcij *Sara Novak, Univerza v Ljubljani, Biotehniška fakulteta*
14.40-15.00	Odmor

Ocena tveganja izpostavljenosti delcem in zakonodaja Moderatorka: Viviana Golja	
15.00-15.20	Zakonodajni aspekt izpostavljenosti delcem *Anja Menard Srpčič, Urad za kemikalije, Ministrstvo za zdravje*
15.20-15.40	Chemical regulation in Europe: focus on nanomaterials *Andrej Kobe, DG Environment, European Commission*
15.40-16.00	Ocena tveganja za zdravje ljudi zaradi izpostavljenosti nanodelcem iz okolja *Viviana Golja, Nacionalni inštitut za javno zdravje*
16.00-16.20	Challenges in extracting information from peer-reviewed scientific articles to be used for risk assessment *Ana Maria Rincon, EFSA*
16.20-16.40	Challenges in oral toxicity studies for the risk assessment of titanium dioxide in food *Walter Brand, RIVM*
16.40-16.50	Odmor
16.50-17.30	Odgovori na vprašanja, zaključne misli

POVZETKI VABLJENIH PREDAVANJ

Mikro- in nanodelci ter biološki sistemi I

Nanomedicine in Europe: Applications and Challenges

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Keywords: nanomedicine, nanotechnology, clinical translation, ETPN

Medicine is undergoing a major transformation, which is described by the term "precision medicine". This refers to the combination of more precise diagnostics with increasingly targeted and efficient therapies. New active substances and new materials ("advanced materials", especially nanoscale materials), in combination with future technologies such as communication technologies, artificial intelligence, digitalisation and databases (big data), will make it possible to treat patients more and more individually ("personalised medicine"). And nanomedicine, i.e. the application of nanotechnology in medicine, is already a reality in many medical practices. Nanopharmaceuticals (NPh) have attracted tremendous interest in the pharmaceutical field in the last decade. Many companies, including SMEs focused on R&D, as well as multinational companies like Pfizer, Eli Lilly and Company, Novartis, Astra Zeneca and Sanofi, have been actively developing NPh formulations over the past years, investing billions of dollars, either in developing their own pipeline or through acquisitions. Thanks to the investment and to the efforts in innovations, the nanopharmaceutical field is continuously evolving. Currently, >100 nanoparticle-based products are in clinical trials, of which 18 ongoing clinical trials have been started in the last three years to evaluate completely new NPh concepts. One important measure in the EU to support this growth is the European Technology Platform Nanomedicine (EPN), which is a network of experts along the whole value chain of nanomedicine and related fields. This presentation will provide an overview of current nanomedical applications and their research and commercialisation in Europe.

Upravljanje s tveganji povezanimi z nanomateriali: predstavitev H2020 NMBP-13 projektov

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Ključne besede: nanotehnologija, nanotoksikologija, gradniki upravljanja s tveganji, pripravljenost/zrelost nanotoksikoloških podatkov, upravljanje s podatki

Skupina projektov na temo »Upravljanje s tveganji v nanotehnologiji« (NMBP-13), ki jo financira Evropska komisija, je zasnovana tako, da ustvarja gradnike za upravljane s tveganji in uporablja rezultate številnih predhodno financiranih projektov na tem področju. Upravljanje se nanaša na procese, "s katerimi se družba in gospodarstvo upravljata kolektivno". Upravljanje s tveganji temelji na načelih dobrega upravljanja, kot so vključevanje, sprejemanje odgovornosti, preglednost, odzivnost, pravičnost, učinkovitost in visoka storilnost in upoštevanje vladavine prava za identifikacijo, vrednotenje, upravljanje tveganj in komuniciranje o le teh. Cilj obvladovanja tveganj je pomagati vsem interesnim skupinam pri sprejemanju boljših odločitev. Na tem področju je potrebno tudi zaupanje tako znotraj strokovne skupnosti kot tudi med širšo javnostjo in potrošniškimi skupinami. Upravljanje s tveganji se mora osredotočiti predvsem na znanje o tveganjih, tj. znanje o negotovost. Pomemben vidik zanesljivosti upravljanja s tveganji je povezan s podatki/informacijami in vedenjem na tem področju. Problem, ki ga obravnavajo projekti iz skupine NMBP-13 je, kako preoblikovati tako zapleten sistem podatkov, informacij in znanja, pomembnega za obvladovanje tveganj povezanih z nanomateriali, v funkcionalno znanje za sprejemanje odgovornih odločitev. Toda znanje ni le rezultat avtomatiziranega zbiranja informacij. Znanje izhaja iz veliko bolj zapletenega procesa, ki je vezan na družbo in kulturo. Znanje je potrebno za razvoj, vrednotenje in prilagajanje odločitev in možnosti odločanja. To pomeni, da je znanje nujen element človekove interakcije z resničnim svetom v procesu odločanja. Eden od pomembnejših projektov na področju upravljanja tveganj povezanih z nanomateriali je NANORIGO, ki obravnava vprašanja o tem, kako pripraviti informacije iz množice podatkov in kako oblikovati ustrezno vedenje za sprejemanje odločitev tveganj v praksi.

Nano risk governance: contribution by H2020 NMBP-13 projects

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Keywords: nanotechnology, nanotoxicology, risk governance architecture, nanotoxicology data readiness level, data management

The group of “Risk Governance of Nanotechnology” projects (H 2020 NMBP-13), funded by the European Commission, is designed to create a risk governance architecture and leverage the results from many previously funded projects in the area of nanomaterial hazards and risks. Governance refers to the structures and processes "through which society and the economy are collectively governed." Risk governance applies the principles of good governance such as participation, accountability, transparency, responsiveness, equity and inclusion, effectiveness and efficiency, rule of law to the identification, assessment, management and communication of risks. The goal of risk governance is to help stakeholders make better decisions and to build a higher level of trust, both within the expert community and among the broader public and consumer groups. Risk governance needs to focus primarily on knowledge about risk, i.e., knowledge about possible futures and uncertainty about which of those futures will actually occur. An important aspect of reliability in risk governance relates to data/information and knowledge readiness or maturity. The problem addressed by the NMBP-13 projects is how to transform such a complex system of data, information and knowledge relevant to nanomaterial risk management into functional knowledge for decision making and governance of (nano)materials risks. Knowledge, is an element of potential. But knowledge is not just a result of filtering or algorithms. It results from a much more complex process that is social, goal-oriented, context-dependent and culturally bound. Knowledge is needed to develop, evaluate, and adjust decisions and decision options. This means that knowledge is a necessary element of human interaction with the real world during the decision-making process. One of the highly engaged projects in the area of nanorisk governance is NANORIGO, which addresses overarching questions around the readiness of inputs to risk governance as a practice.

Varnost nanodelcev anorganskih UV filtrov v kozmetičnih izdelkih

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Ključne besede: cinkov oksid, koža, nanodelci, titanov dioksid, toksičnost, UV zaščita

Nanodelci titanovega dioksida (TiO_2) in cinkovega oksida (ZnO) so učinkoviti UV filtri, ki ščitijo kožo pred škodljivimi vplivi UVA in UVB sevanja, zato so pogosta sestavina sodobnih kozmetičnih izdelkov. Njihova ključna prednost pred večjimi delci anorganskih UV filtrov je boljša estetska sprejemljivost kozmetičnih izdelkov z nanodelci zaradi transparentnega sloja, ki ostane na koži po nanosu izdelka. Kljub široki uporabi pa je še vedno aktualno vprašanje o njihovi varnosti. Zaradi specifičnih lastnosti, ki so odraz nanometrske velikosti, lahko nanodelci v organizmu sprožajo nastajanje reaktivnih kisikovih zvrsti in povzročajo neželene učinke. Da se neželenim učinkom izognemo, so bistvene ustrezno načrtovane lastnosti nanodelcev (velikost, oblika, površinske lastnosti) in sestavine podlage kozmetičnega izdelka, v katerega so nanodelci vgrajeni. Raziskave *in vitro* kažejo, da so nanodelci TiO_2 v primerjavi z nanodelci ZnO bolj varni. Razlog je razlika v topnosti, in sicer so nanodelci ZnO bolje topni in povzročajo citotoksične učinke zaradi spodbujanja oksidativnega stresa in rušenja homeostaza Zn^{2+} ionov. Omenjeni učinki nastopijo le, če nanodelci po dermalnem nanosu dosežejo žive celice kože. Ker je zdrava koža učinkovita bariera, ki preprečuje vstop nanodelcev v ali skozi kožo, je verjetnost neželenih učinkov nanodelcev anorganskih UV filtrov v primerjavi z dokazanimi koristmi, ki jih prinaša uporaba kozmetičnih izdelkov za zaščito pred soncem, majhna. Pri uporabi kozmetičnih izdelkov pa je pomemben tudi vidik nedermalne izpostavljenosti med uporabo kozmetičnih izdelkov z nanodelci anorganskih UV filtrov (pulmonalna izpostavitev), ki dokazano povzroča citotoksične učinke. Tako je ključnega pomena pravilna uporaba kozmetičnih izdelkov, s katero preprečimo potencialni vnos v pljuča. V predavanju bodo predstavljene lastnosti nanodelcev anorganskih UV filtrov, ki so povezane s sprožanjem neželenih učinkov, potencialni toksični učinki, ki jih nanodelci povzročajo, in lastnosti kožne bariere, ki so bistvene za preprečevanje toksičnosti pri dermalni uporabi.

Safety of nanoparticulate inorganic UV filters in cosmetics

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Keywords: zinc oxide, skin, nanoparticles, titanium dioxide, toxicity, UV protection

Nanoparticulate titanium dioxide (TiO_2) and zinc oxide (ZnO) are effective inorganic UV filters, thus they are frequently used in the modern cosmetic products. Their advantage over larger particles of inorganic UV filters is better aesthetic acceptability of cosmetic products with incorporated nanoparticles, as the layer that remains on the skin after application of the cosmetic product is translucent. Despite their widespread use, their safety is still under the question. Due to their special properties, which are attributed to their nanometer size, nanoparticles can trigger in the body the formation of reactive oxygen species and cause unwanted side effects. The design of nanoparticles with optimal properties (size, shape, surface characteristics) and the selection of suitable vehicle of cosmetic product in which they will be applied are thus crucial to avoid such unwanted effects. In vitro studies have shown that TiO_2 nanoparticles are safer than ZnO nanoparticles. The reason is the difference in solubility, namely ZnO nanoparticles are more soluble and cause cytotoxic effects due to the generation of oxidative stress and disruption of Zn^{2+} ion homeostasis. These effects only occur if nanoparticles reach living skin cells after dermal application. The healthy skin is an effective barrier that prevents penetration of nanoparticles into or through the skin, thus the probability of side effects caused by nanoparticulate inorganic UV filters is low compared to the proven benefits of sunscreen use. However, the non-dermal exposure (pulmonary) to nanoparticulate inorganic UV filters associated with the use of cosmetic products is important, since it has been proven to cause cytotoxic effects. Thus, the correct use of cosmetic products is crucial to prevent the potential pulmonary exposure. In the scope of the lecture, the properties of nanoparticulate inorganic UV filters, which are associated with their side effects, the potential toxic effects caused by nanoparticles, and the skin barrier properties that are essential to prevent toxicity in dermal use will be discussed.

Nanodelci, ki jih odpuščajo celice v svojo okolico: lipoproteinski koloidi s prehodno identiteto (mikrovezikli) in stabilni nanosomi (eksosomi)

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Ključne besede: koloidni vezikli, eksosomi, brstenje celične membrane, microalgae, nanoalgosomi

Pri preučevanju celičnih nanodelcev se je uveljavila delitev na tri tipe delcev: apoptotska telesca, mikrovezikle in eksosome. Prvi naj bi nastali ob razpadu celice v z membrano obdane fragmente, drugi pri brstenju plazemske membrane, tretji pa v endosomih, ki naj bi nastale nanodelce po zlitju s plazemsko membrano odpustili v okolno raztopino. Obstoječe metode zaznajo v izolatih delce velikosti med 20 in 1000 nm z raznoliko sestavo (več sto vrst proteinov). Pri preučevanju izolatov iz sveže krvi, dobljenih s centrifugiranjem in izpiranjem vzorcev, smo ugotovili, da gre predvsem za nekaj sto nanometrov velike fragmente trombocitov in eritrocitov celic, ki nastanejo med procesiranjem vzorcev zaradi strižnih sil. V izolatih iz starane krvi smo našli nativne, z membrano obdane delce velikosti med 50 in 100 nm. Mikrografi brstečih eritrocitov kažejo, da gre za mikrovezikle, ki se formirajo na vrhu ehinocitnih izrastkov. V izolatih iz mikroalgnih medijev zaznane celične nanodelce smo poimenovali »nanoalgosomi«. Z nanoalgosomi bogati izolati kažejo morfologijo, ki se razlikuje od eritrocitnih mikroveziklov. Naši rezultati podpirajo hipotezo, da so nanoalgosomi v izolatih v celici nastali delci – eksosomi.

Nanoparticles shed by cells in their surroundings: lipoprotein colloids with transient identity (microvesicles) and stable nanosomes (exosomes)

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Keywords: colloid vesicles, exosomes, cell membrane budding, microalgae, nanoalgosomes

In the study of cellular nanoparticles, division into three types of particles has been established: apoptotic bodies, microvesicles, and exosomes. The first are thought to form when the cell disintegrates into membrane-surrounded fragments, the second during budding of the plasma membrane, and the third in endosomes, supposedly being released into the surrounding solution after fusion of the endosome with the plasma membrane. Existing methods detect in isolates particles between 20 and 1000 nm in size with a diverse composition (hundreds of types of proteins). In the study of fresh blood isolates obtained by centrifugation and washing of samples, we found mainly several hundred nanometer-sized fragments of platelets and erythrocytes that were formed during sample processing due to shear forces. In aged blood isolates, native, membrane-bound particles between 50 and 100 nm were found. Micrographs of budding erythrocytes indicate that these are microvesicles that form at the top of echinocyte spicules. The cellular nanoparticles detected in microalgal media isolates were called "nanoalgosomes". Nanoalgosome-rich isolates show a morphology different from erythrocyte microvesicles. Our results support the hypothesis that nanoalgosomes in isolates are particles that were formed inside the cells - exosomes.

POVZETKI VABLJENIH PREDAVANJ

Mikro- in nanodelci ter biološki sistemi II

Inhalational exposure to nanoparticles in workers monitored using oxidative stress markers

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Keywords: nanoparticles, biomonitoring, exhaled breath condensate, oxidative stress

Introduction: Human health data regarding exposure to nanoparticles are extremely rare and biomonitoring of workers´ exposure is lacking in the practice. However, experimental data point to oxidative stress and cellular damage. Especially little is known about complex mixtures of nanoparticles and their interactions with the long-term exposure, physical load, and lifestyle. Methods: Aerosol exposures were monitored during the working operations using a suite of real-time and integrated instruments: plant A – nanoTiO_2 and Fe-oxides pigments production; plant B - nanomaterials research and machining. In plant A, 48 workers and 65 controls were examined in 2012 and 2013; in plant B, total 61 researchers were examined in 2016, 2017 and 2018, with comparable 62 controls. Panels of oxidative stress biomarkers derived from free radical oxidation of lipids, nucleic acids, and protein damage were analyzed in exhaled breath condensate (EBC) and in urine by LC-ESI-MS/MS: malondialdehyde (MDA), 4-hydroxy-trans-hexenal (HHE), 4-hydroxy-trans-nonenal (HNE), aldehydes C6-C13, 8-isoProstaglandinF2α (8-isoprostane); 8-hydroxy-2-deoxyguanosine (8-OHdG), 8-hydroxyguanosine (8-OHG), 5-hydroxymethyl uracil (5-OHMeU); o-tyrosine (o-Tyr), 3-chlorotyrosine (3-ClTyr), and 3-nitrotyrosine (3-NOTyr). Additionally, plasma samples were analyzed in plant B. Results: Median mass concentration in the workshops ranged from 0.083 to 1.840 mg/m^3, total particle number concentration from $1.98x10^4$ to $5.4x10^5$/cm^3. Nanoparticles accounted for 40-96%. Markers of nucleic acids and proteins oxidation were elevated already in the pre-shift samples ($p<0.05$) of the workers relative to controls. Markers of lipid oxidation showed a significant post-shift increase ($p<0.05$). Conclusion: Markers of lipids oxidation reflect acute exposures (cross-shift), while markers of oxidation of nucleic acids and proteins show chronic oxidative stress. Among the fluids examined, EBC appeared the most valuable source, followed by plasma; least sensitive was urine. Long-term nanoparticle exposures caused lung function impairment. Monitoring of both effects using EBC biomarkers of oxidative stress (for example MDA and 8-OHdG) and spirometry are methods of choice.

Epidemiološka dognanja o vplivu nano in mikro delcev na zdravje ljudi

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Ključne besede: nano in mikro delci, epidemiologija, vpliv na zdravje, pljuča, princip analogije

Poglavja časovnice raziskovanja vpliva nanodelcev na zdravje so: toksikologija, metrologija, ocena izpostavljenosti, tehnološki nadzor in osebna varovalna sredstva, ocena tveganja, upravljanje s tveganjem, zdravstveni nadzor in epidemiološko raziskovanje. Največ je toksikoloških raziskav, izjemno pa je pomanjkanje študij analitičnih standardov, metod določanja izpostavljenosti, posledično tudi epidemioloških raziskovanj. Cilj slednjega je izpostavljenost vzročno povezati s posledico, najpogosteje boleznijo. Obstajajo le redke epidemiološke študije, ki pa povezujejo izpostavljenost z biomarkerji in vključujejo majhno število delavcev. Časovnica intenzivnega raziskovanja v epidemiologiji nanodelcev je omejena na zadnjih 10 let in je skopa. Prvi problem vzročnih epidemioloških študij predstavlja dobra ocena izpostavljenosti, kjer pa še ni jasno, kako naj se meri: s številom nanodelcev na volumsko enoto in/ali številom aglomeratov, strukturo in morfologijo delcev, kumulativno dozo... Kritični organ so pljuča, nanodelci, predvsem zaradi svoje velikosti, lahko nemoteno penetrirajo globoko v alveolarni prostor. Epidemiološke študije so pokazale jasne vnetne učinke PM10, PM2,5 in manjših delcev od 2,5µm. V epidemiološkem raziskovanju tega vpliva nas vodi predvsem princip analogije po katerem sklepamo, da čim manjši so prašni delci, večji in resnejši je vpliv teh na tarčni organ, to je pljuča. Vnetni proces v pljučih vpliva tudi na kardiovaskularno funkcijo. Drugi dve poti vnosa sta dermalna in oralna. Epidermis, dermis in hipodermis naj bi predstavljala dobro bariero za okoljske polutante, čeprav naj bi bili prašni delci, ki nastanejo zaradi prometa in saje, odgovorni za staranje kože in spremenjeno pigmentacijo. Onesnažen zrak naj bi povzročil nastanek raka kože, prašni delci pa naj bi delovali kot vektor prenosa karcinogenov, kot je npr. benzo-a-piren. Vnos delcev s hrano gre pretežno na račun kvalitete zemlje, kot tudi predpisanih dovoljenih mejnih vrednosti kontaminantov v ribah, kmetijskih pridelkih in mesu. Za tak vnos in možen vpliv na zdravje ljudi ni epidemioloških podatkov, zato tudi ni pravil, ki bi tak vnos omejevala. Podobno je s pitno vodo.

Epidemiological evidence of the impact of nano- and microparticles on human health

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Keywords: nano- and microparticles, epidemiology, impact on health, lung, principle of analogy

The nanoparticle health impact research timeline consists of toxicology, metrology, exposure assessment, technological control and personal protective equipment, risk assessment, risk management, health surveillance, and epidemiological research. Toxicology research is the most extensive, but there is a lack of studies on analytical standards, methods for determining exposure, and, consequently, epidemiological research. Such research aims to causally link exposure to a consequence, most often a disease. There are few epidemiological studies that link exposure to biomarkers and involve a small number of workers. Intensive research in nanoparticle epidemiology is limited to the last 10 years and is scant. The first problem for causal epidemiological studies is a good estimation of exposure, but it is not yet clear how to measure it. The critical organ is the lung, where nanoparticles can penetrate deep into the alveolar space. Epidemiological studies have shown clear inflammatory effects of PM10, PM2.5, and particles smaller than 2.5 µm. Epidemiological research into this effect is primarily guided by the principle of analogy, which suggests that the smaller the particulate matter, the greater the impact on the target organ—that is, the lung. The inflammatory process in the lungs also affects cardiovascular function. The other two routes of intake are dermal and oral. The skin is believed to provide a good barrier to environmental pollutants, although traffic-generated dust particles and soot are thought to be responsible for skin ageing and altered pigmentation. Air pollution is believed to cause skin cancer, and dust particles are thought to act as a vector for the transmission of carcinogens such as benzo[a]pyrene. The intake of particulate matter through food largely depends on soil quality. There are no epidemiological data on such intake and the potential impact on human health. The situation is similar for drinking water.

Toksični učinki nano- in mikrodelcev

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Ključne besede: nanodelci, mikrodelci, toksičnost, škodljivi učinki

Nano- in mikromateriali se pogosto uporabljajo zaradi njihovih edinstvenih mehanskih, kemijskih in optičnih lastnosti, vendar pa ostaja skrb glede njihovega morebitnega vpliva na zdravje ljudi. Ljudje so lahko izpostavljeni nano- in mikrodelcem primarno oralno, z inhalacijo, dermalno ali pa parenteralno.
Nano- in mikrodelci imajo lahko toksične učinke na človeški organizem in zdravje. Rezultati raziskav kažejo, da so toksični učinki nano- in mikrodelcev odvisni od njihove velikosti, oblike, geometrije, hidrofobnosti in naboja, saj te površinsko-kemijske lastnosti vplivajo na njihovo interakcijo s celico in absorpcijo ter tudi od njihovega odmerka. Kronična izpostavljenost in visoki odmerki verjetno povzročajo večje prehajanje v celice in s tem večjo toksičnost
Raziskave, v katerih so preučevali morebitne toksične učinke nano- in mikrodelcev, so bile izvedene večinoma na poskusnih živalih in na in vitro celičnih kulturah. Nano- in mikrodelci povzročajo toksičnost pri živalih ali človeških celicah predvsem zaradi oksidativnega stresa, energijske presnove, metabolizma lipidov, vnetja in zaviranja acetilholinesteraze, kar vodi do spremembe vedenja celic, zmanjšanja rasti, okvare reprodukcije in umrljivosti.

Čeprav so akutno toksičnost nano- in mikrodelcev preučevali v številnih raziskavah, pa je le malo podatkov glede toksičnih učinkov pri dolgotrajni izpostavljenosti. V maloštevilnih raziskavah, v katerih so preučevali subkronične in kronične toksične učinke nanodelcev, so opazovali dolgoročne učinke na zdravje živali, kot so nevrotoksičnost, vpliv na imunski sistem, kardiovaskularno funkcijo, genotoksičnost, karcinogeneza po enkratni in/ali ponavljajoči se kronični izpostavljenosti. Pri tem so opazovali tudi smrtnost in obolevnost. Kronična izpostavljenost anorganskim delcem je bila povezana z motenim izločanjem, vnetjem in fibrozo v pljučih. Ugotovljeno je tudi bilo, da je kopičenje nanodelcev v telesu lahko povezano s karcinogenezo ter boleznimi srca in ožilja.

Pri tem pa rezultati raziskav niso bili konsistentni. Zato so potrebne nadaljnje študije, ki bodo skušale razjasniti potencialne toksične učinke nano- in mikrodelcev predvsem pri ljudeh.

Toxic effects of nano- and microparticles

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Keywords: nanoparticles, microparticles, toxicity, hazardous effects

Nano- and micromaterials have been widely used due to their unique mechanical, chemical and optical properties, however, concerns remain about their potential impact on human health. Humans can be exposed to nano- and microparticles primarily orally, by inhalation, dermally, or parenterally.
It has been suggested that nano- and microparticles have hazardous effects on human organism and health. The results of studies indicate that the toxic effects of nano- and microparticles depend on their size, shape, geometry, hydrophobicity, and their charge since these surface-chemical properties influence their cellular interaction and uptake, as well as on the dose. Chronic exposure and high dose can also lead to higher cellular uptake, therefore causing greater toxicity.
The studies investigating the potential toxic effects have been performed mostly on experimental animals and on in vitro cell culture systems. Nano- and microparticles cause toxicity in animals or human cells mainly through oxidative stress, energy metabolism, lipid metabolism, inflammation and inhibition of acetylcholinesterase, which leads to alternation of cell behaviour, growth reduction, reproductive failure and mortality.

Although acute toxicities of nano- and microparticles have been investigated in many studies, little information is available regarding the log term toxicity. In only few studies investigating subchronic and chronic toxic effects of nanoparticles, the long-term effects on the health of animals such as neurotoxicity, immunotoxicity, influence on cardiovascular function, genotoxicity, carcinogenesis have been evaluated after single and/or repeated chronic exposure. The mortality and morbidity have been also observed. Chronic exposure to nano- and microparticles has been associated with impaired clearance, inflammation and fibrosis in lungs. It has also been found that the accumulation of nanoparticles in the body may correlate with carcinogenesis or cardiovascular disease.

However, the results of the studies have been not consistent. Therefore, further research is needed to elucidate the potential toxic effects of nano- and microparticles, especially in humans.

Nano- in mikroplastika v tleh: raziskave v okviru projekta EU Horizon 2020 Papillons

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Ključne besede: mikroplastika, nanoplastika, kmetijska plastika, kemikalije dodane plastiki, kopensko okolje, ekotoksičnost

Onesnaževanje okolja z nano- in mikroplastiko (NMP) je eno izmed vidnejših okoljskih problemov zadnjega desetletja. Prve raziskave so se osredotočale predvsem na pojavljanje NMP v morskih ekosistemih, precej manj pa je znanega o kopenskem okolju. Nedavne raziskave kažejo, da le-to predstavlja velik ponor in rezervoar NMP. Največji viri onesnaževanja kopenskega okolja z NMP so: kmetijstvo, uporaba odpadnega blata iz čistilnih naprav kot gnojilo, izcedne vode iz cest ter mehanska razgradnja večjih plastičnih odpadkov. V Evropi se letno porabi 3-4 tone kmetijske plastike, kar rezultira v 1 toni odpadkov letno. Glavna uporaba plastičnih materialov v kmetijstvu je v zaščitnih folijah oz. tkaninah, toplih gredah, namakalnih sistemih, folijah za balirano seno, zabojnikih, embalažah za gnojila, ovojih semen, ipd. Med samo uporabo kmetijske plastike na tleh in nepravilnim ravnanjem s plastiko po končani uporabi se lahko večji deli plastike razgradijo do mikro- in nanoplastik. Le te se v okolju nalagajo, kar naj bi imelo zanj dolgoročne posledice. Novi EU Horizon 2020 projekt Papillons (angl. (Plastic in Agricultural Production: Impacts, Lifecycles and LONg-term Sustainability) se bo ukvarjal s tem pomembnim vprašanjem. Glavni cilj projekta je oceniti okoljsko in socialno-ekonomsko vzdržnost uporabe kmetijske plastike glede na njeno potencialno sproščanje v okolje in vplive nanj. V projektu bo sodelovalo 20 partnerjev, med njimi tudi Univerza v Ljubljani. Glavni rezultat projekta bo temeljito poznavanje problematike uporabe kmetijske plastike, kar bo omogočilo podporo inovacijam na področju razvoja trajnostno naravnanih kmetijskih plastik ter podporo implementaciji ustrezne zakonodaje za regulacijo uporabe teh izdelkov ter ravnanja z odpadki. V prispevku bomo predstavili glavne cilje in metodologijo projekta, predvsem pa naloge, ki jih bo v okviru projekta izvajala Univerza v Ljubljani.

Impact of nano- and microplastics on terrestrial environment: EU Horizon 2020 Papillons project

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Keywords: microplastic, nanoplastic, agricultural plastic, plastic chemical additives, soil, ecotoxicity

Nano- and microplastics (NMPs) pollution is a growing global environmental problem. Although the majority of initial focus has been on the marine pollution, terrestrial environment is also heavily polluted with plastics. In fact, it has been proposed that terrestrial environment presents the largest reservoir of plastic particles to be potentially released to other environments. One of the main sources of NMPs to soil is agricultural plastics. Between 3 and 4 Mt agricultural plastics are currently in use in Europe, generating annually 1 Mt waste. Plastic is an important commodity in farming, improving crop protection and performance. It is used in cultivation films (greenhouse, tunnel, covers and mulching films) and micro-irrigation systems, silage, wraps and containers. During use and end-of-life some agricultural plastics degrade and generate fragments including NMPs that can accumulate in soil on a transitory or permanent basis. The long-term impacts of this pollution are unknown. The new EU Horizon 2020 project Papillons (Plastic in Agricultural Production: Impacts, Lifecycles and LONg-term Sustainability) will tackle this important question. The main aim is to elucidate ecological and socioeconomic sustainability of agricultural plastics in relation to releases and impacts of NMPs in European soils. The project will advance the knowledge on sources, behaviour and impacts through cross-disciplinary research performed in 20 international research institutions including University of Ljubljana. The final output will be the creation of knowledge and scientific background to enable policy, agricultural and industrial innovation towards sustainable farm production systems. We shall present the major aims, and methodologies used in the project, and particular the tasks that will be covered by the University of Ljubljana.

Odstranjevanje monomerov plastike iz okolja z naprednimi oksidativnimi metodami

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Ključne besede: napredni oksidacijski procesi, heterogena fotokataliza, plazmonske kovine, Au+TiO_2 fotokatalizatorji, hormonski motilci, bisfenoli

Rast prebivalstva, razvoj industrije in podnebne spremembe spadajo med poglavitne vzroke za povečano porabo pitne vode. Kljub temu je dandanes ponovna uporaba izrabljene vode še vedno zelo omejena. Za potrebe čiščenja odpadnih voda je bil v zadnjih desetletjih velik interes posvečen razvoju kemijskih oksidacijskih postopkov, klasificiranih kot napredni oksidacijski postopki (AOPs)[1]. Eden izmed najbolj preučevanih postopkov za čiščenje odpadnih voda je heterogena fotokataliza, kjer je glavna vloga fotokatalizatorja (najpogosteje polprevodnega TiO_2), da ob obsvetljevanju s svetlobo tvori kisikove reaktivne zvrsti (ROS). Le-te se nadalje uporabljajo za razgradnjo v vodi raztopljenih organskih onesnažil v H_2O in CO_2 (mineralizacija). Kombiniranje TiO_2 in plazmonske kovine (npr. Au) omogoča sprožitev katalitske aktivnosti TiO_2 tudi pri obsvetljevanju z vidnim spektrom svetlobe zaradi generiranja in vbrizgavanja/prenosa "vročega elektrona", prenosa energije plazmonske resonance in plazmonskega ogrevanja[2]. Bisfenol A (BPA) se uporablja pri proizvodnji polikarbonatne plastike, epoksidnih smol in termo papirja. Yamamoto in sodelavci[3] so zaznali BPA v sedmih od desetih preučevanih vzorcev izcednih voda iz odlagališč smeti. Zaradi endokrinih učinkih BPA poskuša industrija le-tega nadomestiti z bisfenolom AF (BPAF), S (BPS) in F (BPF).
Poglavitna cilja študije sta bila: (i) podrobno raziskati, kako morfološke lastnosti in zeta potencial TiO_2 nosilcev (nanodelci (TNP) in nanopalice (TNR)) vplivajo na optične, elektronske in fotokatalitične lastnosti TiO_2+Au kompozitov ter (ii) izvajanje heterogenih fotokatalitskih testov z vidnim spektrom svetlobe v prisotnosti TiO_2+Au kompozitov za razgradnjo vodnih raztopin različnih bisfenolov (BPA, BPAF, BPS in BPF).

Rezultati eksperimentov so pokazali, da je kompozit TNR+Au ob obsvetljevanju z vidnim spektrom svetlobe ustvaril največjo množino nosilcev naboja in ROS, ki so bili nadalje uspešno uporabljeni za mineralizacijo v vodi raztopljenih bisfenolov. Uporabo nadomestkov BPA je potrebno ponovno premisliti, saj BPAF in BPS v primerjavi z BPA izkazujeta večjo odpornost proti oksidaciji z ROS.

[1]R. Andreozzi et al., Catal. Today, 1999, 53, 51-59; [2]W. Hou et al., Adv. Funct. Mater., 2013, 23, 1612-1619; [3]T. Yamamoto et al., Chemosphere, 2001, 42, 415-418.

Removal of plastic monomers from the environment by advanced oxidation processes

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Keywords: advanced oxidation processes, heterogenous photocatalysis, plasmonic metals, Au+TiO_2 photocatalysts, endocrine disrupting chemicals, bisphenols

Population growth, industry development and climate change are the main reasons that every year increasing quantities of fresh water are used. Nowadays, very limited reuse of spent water takes place. In the last decades, a group of chemical oxidative technologies classified as advanced oxidation processes (AOPs) have received significant interest as applications in wastewater treatment[1]. One of the most studied AOPs for wastewater treatment is heterogeneous photocatalysis, where the main role of a catalyst (mostly semiconductor TiO_2) upon light illumination is to produce reactive oxygen species (ROS). ROS are further used for the transformation of liquid-dissolved organic pollutants into H_2O and CO_2 (mineralization). Combining the TiO_2 with a plasmonic metal (e.g. Au) can enhance the visible-light interaction of TiO_2 through scattering, absorption, sensitization and hot electron injection[2]. Bisphenol A (BPA) is used for the production of polycarbonate plastic, epoxy resins and thermal paper. Yamamoto et al.[3] reported that BPA was detected in seven out of ten investigated landfill leachates. Due to its controversial endocrine-disrupting effects, the industry attempts to substitute BPA by bisphenol AF (BPAF), S (BPS) and F (BPF).

The aims of the study were: (i) to investigate in detail how the textural properties and the zeta potential of TiO_2 supports (nanoparticles (TNP) and nanorods (TNR)) influence the optical, electronic and photocatalytic properties of plasmonic-based TiO_2+Au composites, and (ii) to conduct photocatalytic tests in presence of TiO_2+Au composites under visible-light illumination using water-dissolved bisphenols (BPA, BPAF, BPS and BPF) as model organic pollutants.

The results of photocatalytic oxidation experiments revealed that TNR+Au composite generated the highest amount of charge carriers and ROS, which were successfully used for oxidation and mineralization of water-dissolved bisphenols. Further, the use of BPA substitutes should be reconsidered as both BPAF and BPS expressed higher resistance toward the oxidation with ROS.

[1]R. Andreozzi et al., Catal. Today, 1999, 53, 51-59; [2]W. Hou et al., Adv. Funct. Mater., 2013, 23, 1612-1619; [3]T. Yamamoto et al., Chemosphere, 2001, 42, 415-418.

POVZETKI VABLJENIH PREDAVANJ

Metode za vrednotenje nanodelcev

Can we make data sharing less painful? - The Metadata Shepherd

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Keywords: data management, data life cycle, FAIR data sharing, metadata standards and completeness

There is general agreement that sharing data will speed up scientific innovation and public sharing is now required in many public funding programmes. For the nanosafety area in particular, a steadily increasing amount of new nano-specific methods for physicochemical, hazard, exposure and fate characterisation and their combination into integrated testing strategies to replace animal testing and the emergence of nanoinformatics as a key component of nanotechnology and nanosafety assessment for grouping and read-across have put the spotlight firmly on the need for access to high-quality, curated datasets. To date, the focus has been around what constitutes data quality and completeness and on the development of minimum reporting standards. Concepts like the FAIR principles (Findable, Accessible, Interoperable and Re-usable) define high-level goals but moving from the theoretical realm to practical implementation puts a lot of additional workloads onto data curators and often leads to the fact that central data management and sharing is done at the very last minute or not done at all. Important metadata explaining the experiment and describing the details of the experimental procedure have then to be recovered from different documents including lab notebooks and supplier information or are completely lost.

One of the main reasons why data sharing and the needed data management to enable it is perceived as painful is that it is seen as an additional task outside of the normal laboratory practice. It is most often also not clear who is in charge to provide the metadata in a form that it can be shared with others. To circumvent this, the definition of clear roles and responsibilities across the complete data lifecycle is needed to reach a deeper appreciation of what metadata is, and how to capture and index it[1]. The H2020 NanoCommons infrastructure project (https://www.nanocommons.eu/) develops approaches and provides training and consultancy in form of Transnational Access offers on how to unify all nano-community efforts to define metadata standards and schemas and to organise the data management cycle as a joint effort of all players (data creators, analysts, curators, managers, and customers) supervised by the newly defined role of data shepherd. This is supported by new technical solutions helping to integrating data management directly in the data production process at the earliest possible state, in this way, generating FAIR nanosafety data as part of the standard procedure und making the advantages of harmonised and interoperable data available to the original user as well as re-user of the data.

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Metode določanja lokalizacije in kemijske oblike nanodelcev kovin in kovinskih oksidov v rastlinskih tkivih

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Ključne besede: slikovne tehnike, rastline, nanodelci, rentgenska spektometrija, masna spektrometrija

Nanodelci kovin in kovinskih oksidov po izpustu v okolje prihajajo tudi v stik z rastlinami. Ker rastline predstavljajo temelj prehranjevalnih spletov, je zato nujno poznavanje mehanizmov privzema in strupenosti nanodelcev kovin in kovinskih oksidov v sistemu tla/substrat-rastlina. V prispevku bomo predstavili metode na osnovi rentgenske svetlobe (mikro-rentgensko fluorescenčna spektrometrija, mikro-XRF; rentgensko absorpcijska spektrometrija, XAS) in masne spektrometrije (lasersko ablacijska spektrometrija s sklopljeno plazmo, LA-ICP-MS) za določanje lokalizacije in kemijske oblike nanonedelcev kovin in kovinskih oksidov v povezavi z mehanizmi strupenosti in biotransformacijo v rastlinskih tkivih.

Methods for determining localization and chemical form of metal nanoparticles and metal oxides in plant tissues

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Keywords: imaging, plants, nanoparticles, X-ray spectrometry, mass spectrometry

After their release into the environment, nanoparticles of metals and metal oxides frequently come into contact with plants. As plants form the basis of food nets, it is necessary to better understand the uptake and toxicity of metal nanoparticles and metal oxides in the soil/ substrate-plant systems. The methods based on X-ray (micro-X-ray fluorescence spectrometry, micro-XRF, X-ray absorption spectroscopy, XAS) and mass spectrometry (laser ablation inductively coupled mass spectrometry, LA-ICP-MS) to determine the localization and chemical forms of metal and metal oxide nanoparticles in relation to toxicity and biotransformation in plant tissues will be presented.

Uporaba vrstične elektronske mikroskopije za raziskave bio-nano interakcij

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Ključne besede: titanovi nanodelci, kobalt feritni nanodelci, volframove nanofibrile, nevretenčarji, mikroskopija, spektroskopija

Uporaba vrstične elektronske mikroskopije (SEM) v kombinaciji z energijsko disperzivno rentgensko spektroskopijo (EDX) in pristopom fokusiranega ionskega žarka (FIB) se vse pogosteje uporablja pri raziskovanju interakcij celic z nanomateriali. Internalizacijo nanomaterialov je mogoče oceniti tudi z uporabo detektorja povratnega sipanja elektronov (BSE), ki je del vrstičnega elektronskega mikroskopa. V delu Novak in sod.[1]smo predstavili uporabo SEM/EDX za opazovanje odstotka adsorbiranih nanodelcev (ND) na telesno površino poskusnih živali. Vodne bolhe vrste *Daphnia magna* so bile v standardnem in modificiranem testu akutne toksičnosti izpostavljene TiO_2 ND. Večji del telesne površine živali, izpostavljenih koncentracijama 10 in 100 mg/L, je bil prekrit z večjimi agregati. Analize EDX so potrdile, da je bil opaženi material Ti. V študiji Novak in sod.[2] smo preučevali morfologijo tkiva prebavnih žlez izopodnih rakov vrste *Porcellio scaber,* hranjenih z nanofibrilami WOx (nano-WOx). V prebavnih žlezah živali, hranjenih s 5000 µg nano-WOx /g suhe hrane, smo na površini nekaterih celic s SEM opazili vlaknaste strukture. Analiza sestave vlaken z EDX je pokazala prisotnost volframa. Prednost metode FIB/SEM pred drugimi razpoložljivimi tehnikami pri raziskovanju kancerogeneze je bila predstavljena v delu Erman in sod.[3] Cilj naše študije je bil vzpostaviti model ortotopskega tumorja mišjega mehurja in raziskati zgodnje faze implantacije rakavih celic MB49 *in vivo,* z različnimi tehnikami označevanja in mikroskopiranja. Za identifikacijo rakavih celic smo uporabili $CoFe_2O_4$ ND. Po prerezu rakavih celic s pomočjo FIB, je EDX analiza vidnih vključkov potrdila prisotnost ND. Kombinacija pristopov FIB/SEM/EDX se je izkazala za uporabno v študijah bio-nano interakcij.

[1]Novak S, Kokalj AJ, Hočevar M, Godec M, Drobne D. The significance of nanomaterial post-exposure responses in Daphnia magna standard acute immobilisation assay: Example with testing TiO2 nanoparticles. Ecotoxicology and environmental safety. 2018 May 15;152:61-6; [2]Novak S, Drobne D, Vaccari L, Kiskinova M, Ferraris P, Birarda G, Remškar M, Hočevar M. Effect of Ingested Tungsten Oxide (WO x) Nanofibers on Digestive Gland Tissue of Porcellio scaber (Isopoda, Crustacea): Fourier Transform Infrared (FTIR) Imaging. Environmental science & technology. 2013 Oct 1;47(19):11284-92; [3]Erman A, Kapun G, Novak S, Pavlin M, Dražić G, Drobne D, Veranič P. How cancer cells attach to urinary bladder epithelium in vivo: study of the early stages of tumorigenesis in an orthotopic mouse bladder tumor model. Histochemistry and cell biology. 2019 Mar;151(3):263-73.

Scanning electron microscopy for studying bio-nano interactions

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Keywords: titanium nanoparticles, cobalt ferrite nanoparticles, wolfram nanofibers, invertebrates, microscopy, spectroscopy

The combination of scanning electron microscope (SEM) with energy-dispersive X-ray spectroscopy (EDX) and the focused ion beam (FIB) approach is increasingly used in investigating the interactions of cells with nanomaterials. Internalized nanomaterials can be assessed also by imaging the sectioned surface using backscattered electrons (BSEs). In work of Novak et al (2018) we presented the use of SEM/EDX for observing the percentage of adsorbed nanoparticles (NPs) on body surface of exposed animals. Daphnids were exposed in standard and modified acute toxicity test to TiO_2 NPs. The larger part of body surface of the daphnids exposed to 10 and 100 mg/L was covered with large aggregates. The EDX analyses confirmed that the observed material was Ti. In another study the morphology of digestive gland tissue of WOx nanofibers (nano-WOx) fed invertebrate *Porcellio scaber* was investigated (Novak et al 2013). In the digestive glands of animals fed with food contaminated with 5000 μg nano-WOx/g of food, fiber-like structures were observed on the surface of some cells. We analyzed these structures with EDX and the chemical composition revealed the presence of tungsten. The advantage of FIB/SEM method over other available techniques in investigating cancerogenesis was presented in work of Erman et al (2019). The aim of our study was to establish an orthotopic mouse bladder tumor model and to explore early stages of implantation of cancerous MB49 cells *in vivo* using various labeling and microscopic techniques. $CoFe_2O_4$ NPs were internalized to unequivocally discriminate cancer cells from normal cells. FIB/EDX demonstrated that the attached cells on the urothelial surface were MB49 cells with internalized NPs. The combined approaches of FIB/SEM/EDX has proven to be applicable in the studies of bio-nano interactions.

[1]Novak S, Kokalj AJ, Hočevar M, Godec M, Drobne D. The significance of nanomaterial post-exposure responses in Daphnia magna standard acute immobilisation assay: Example with testing TiO2 nanoparticles. Ecotoxicology and environmental safety. 2018 May 15;152:61-6; [2]Novak S, Drobne D, Vaccari L, Kiskinova M, Ferraris P, Birarda G, Remškar M, Hočevar M. Effect of Ingested Tungsten Oxide (WO x) Nanofibers on Digestive Gland Tissue of Porcellio scaber (Isopoda, Crustacea): Fourier Transform Infrared (FTIR) Imaging. Environmental science & technology. 2013 Oct 1;47(19):11284-92; [3]Erman A, Kapun G, Novak S, Pavlin M, Dražić G, Drobne D, Veranič P. How cancer cells attach to urinary bladder epithelium in vivo: study of the early stages of tumorigenesis in an orthotopic mouse bladder tumor model. Histochemistry and cell biology. 2019 Mar;151(3):263-73.

POVZETKI VABLJENIH PREDAVANJ

Ocena tveganja izpostavljenosti delcem in zakonodaja

Zakonodajni aspekti izpostavljenosti delcem

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Ključne besede: zakonodaja, nanomateriali, kemikalije, kozmetični izdelki, izpostavljenost

V vsakdanjem življenju na različne načine prihajamo v stik z nanomateriali. Nanomaterialom smo izpostavljeni preko uporabe v potrošniških izdelkih, na delovnem mestu in tudi preko okolja. Za zagotovitev visoke ravni zaščite zdravja ljudi in okolja pred tveganji, ki jih lahko predstavljajo nanomateriali, v EU obstajajo številne zakonodaje, med katere sodita tudi Uredba REACH[1] in Uredba o kozmetičnih izdelki[2]. Omenjeni zakonodaji v okviru področja uporabe vsebujeta ukrepe, ki pripomorejo k zmanjševanju tveganja, ki izhaja iz izpostavljenosti prebivalstva in okolja v EU nanomaterialom. V okviru postopka registracije snovi po REACH mora podjetje pripraviti oceno kemijske varnosti s katero dokaže, da so tveganja zaradi izpostavljenosti nanomaterialom med proizvodnjo in uporabo nadzorovana in kot del ocene izpostavljenosti razviti scenarije izpostavljenosti, ki so priloga k varnostnemu listu (t.i. razširjeni varnostni list). REACH vsebuje tudi postopek evalvacije snovi znotraj katerega država članica EU pojasni zaskrbljenost, ki lahko izhaja iz izpostavljenosti ljudi in okolja nanomaterialu. Na podlagi zakonodaje za kozmetične izdelke mora podjetje izdelati oceno varnosti kozmetičnega izdelka za človekovo zdravje upoštevajoč med drugim tudi izpostavljenost samemu nanomaterialu. Podjetje mora opraviti tudi priglasitev kozmetičnega izdelka pri čemer mora posredovati informacije glede nanomateriala in razumno predvidljive pogoje izpostavljenosti nanomaterialu. Nanomateriali, ki se uporabljajo v kozmetičnih izdelkih so navedeni v Katalogu nanomaterialov, ki vsebuje tudi informacije o kategoriji kozmetičnega izdelka in razumno predvidljive pogoje izpostavljenosti.

[1]Uredba št. 1907/2006 Evropskega Parlamenta in Sveta z dne 18. decembra 2006 o registraciji, evalvaciji, avtorizaciji in omejevanju kemikalij; https://eur-lex.europa.eu/legal-content/sl/TXT/HTML/?uri=CELEX:02006R1907-20210101;
[2]UREDBA (ES) št. 1223/2009 Evropskega Parlamenta in Sveta z dne 30.novembra 2009 o kozmetičnih izdelkih; https://eur-lex.europa.eu/legal-content/SL/TXT/PDF/?uri=CELEX:32009R1223&from=en

Legislation aspects of the exposure to particles

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Keywords: legislation, nanomaterials, chemicals, cosmetic products, exposure

In everyday life we come into contact with the nanomaterials in different ways. We are exposed to nanomaterials through the use of consumer products, at workplace and via the environment. In the EU numerous legislations exist, including REACH Regulation[1] and Cosmetics Regulation[2], with the aim to ensure a high level of protection of human health and environment from the risks that nanomaterials may pose. Afore mentioned legislations have measures which contributes to the reduction of the risk from the exposure of population and environment in EU to nanomaterials. As part of the registration process under the REACH the company must carry out the chemical safety assessment to demonstrated that the risks from the exposure to nanomaterials during its manufacture and use are controlled and as part of the exposure assessment develop the exposure scenario which is attached to safety data sheet (i.e. extended safety data sheet). REACH also includes the substance evaluation process within which the EU Member State can clarify the concern that may arises from exposure of the people and environment to nanomaterials. Based on the cosmetics legislation the company must carry out the safety assessment of the cosmetic products for human health considering also the exposure to nanomaterial. The company must notify the cosmetic product providing information on nanomaterial and reasonably foreseeable exposure conditions. Nanomaterials used in cosmetic products are listed in the Catalog of nanomaterials which also includes the data on the category of cosmetic products and reasonably foreseeable exposure conditions.

[1]Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH); https://eur-lex.europa.eu/legal-content/en/TXT/HTML/?uri=CELEX:02006R1907-20210101; [2]Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30. November 2009 on cosmetic product; https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32009R1223&from=EN

Nanomateriali v EU kemijski zakonodaji: nedavne spremembe (ter ostale novice)

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Ključne besede: nanomaterial, nanoblika, evropska zakonodaja, REACH, trajnostna strategija za kemikalije

Materialom z delci ali strukturami na 'nano-skali' (1-100nm) pravimo nanomateriali. Pogosti so v naravi in naključnih emisijah, a v zadnjih desetletjih smo se naučili materiale na tej skali tudi načrtno manipulirati, kar lahko dramatično spremeni njihove lastnosti. Te spremembe izkoriščamo v inovativnih produktih, prinašajo pa tudi izzive v zagotavljanju varnega upravljanja s kemikalijami. V 2012 je bilo ocenjeno, da kemijska zakonodaja EU okvirno zadošča, a jo je na mestih potrebno modificirati z nano-specifičnimi dopolnili. Kar nekaj zakonodaje o izdelkih (biocidni pripravki, kozmetični izdelki itd.) vključuje posebne določbe, ki zagotavljajo ustrezno upoštevanje specifičnosti nanomaterialov, nekateri tudi dodatno označevanje. Od januarja 2020 so se začele obvezno uporabljati tudi spremembe ključne EU kemijske zakonodaje REACH. Njihov cilj je zagotoviti, da so v registraciji snovi informacije o lastnostih snovi, ocena kemijske varnosti in smernice o varni uporabi snovi v nano obliki (nanomateriala) enakovredne drugim registriranim snovem. Z zadostno karakterizacijo posameznih nano oblik (velikost in oblika delcev, površina, površinska obdelava) so nato izrecno povezane ustrezne informacije o varnosti. Če informacije niso na voljo, jih je potrebno ustvariti; informacije o snovi v drugi obliki (nano ali ne) se ne smejo implicitno zajemati. Določbe upoštevajo tudi tehnične posebnosti nanomaterialov s spremembami seznama potrebnih študij in pogojev prilagoditev standardnega režima preskušanja. Predstavitev ponuja nekaj razmislekov o trenutnih izzivih izvajanja določb in povezanih dejavnostih.
Predstavitev se dotakne tudi nove strategije za trajnost na področju kemikalij, pomembnega prispevka k ciljem evropskega zelenega sporazuma, njenih glavnih elementov in začetka implementacije.

Nanomaterials in EU legislation: recent developments (and other news)

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Keywords: nanomaterial, nanoform, European legislation, REACH, Chemicals Strategy for Sustainability

Nanomaterials are generally considered as materials with particle sizes or features at nanoscale (e.g. 1-100 nanometres). Abundant in nature or in incidental emissions, we have also learned to effectively manipulate – engineer - the nanoscale in last decades. Resulting material change in properties drives innovation but also presents challenge in ensuring safe and responsible chemical management. While EU chemicals regulation framework was considered fit for purpose in the last 2012 review, introduction of nano-specific provisions in some of the legislation was considered necessary for effectiveness and efficiency. A number of product legislations (biocides, cosmetics, etc.) introduced provisions ensuring adequate consideration of specificities of nanomaterials and in some cases labelling. In 2020, changes of the principle EU chemicals regulation REACH also came into mandatory application. Their objective is to ensure that hazard information, chemical safety assessment and subsequently guidance on safe use on nanoforms (i.e. chemicals that are manufactured, imported or placed on the market as nanomaterials) provided in registration is on par with other registered substances. Sufficient characterisation information (particle size and shape, area, surface treatment) must be provided on registered nanoforms as part of substance identity information, with which relevant safety information is then explicitly associated. If such information is not available, it must be generated and not left implicitly covered by information on bulk chemical substance or another nanoform. Further provisions also address technical specificities of nanomaterials through changes to the list of studies required and adaptation conditions. Implementation is well on the way – presentation provides some interim reflections on the present challenges and the activities to address them.

As an addition, presentation touches upon the new Chemicals Strategy for Sustainability, an important contribution to the objectives of the European Green deal, its main elements and already launched activities.

Ocena tveganja za zdravje ljudi zaradi izpostavljenosti nanodelcem iz okolja

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Ključne besede: nanodelci, ocena tveganja za zdravje, izpostavljenost, fizikalno-kemijska karakterizacija, materiali v stiku z živili

Delci v nano velikosti (1 do 100 nm) so v našem okolju prisotni že od nekdaj. Nastajajo pri vulkanskih izbruhih, peščenih viharjih, erozijah tal, požarih. Tudi ljudje jih nenamerno proizvajamo pri različnih aktivnostih v zunanjem in notranjem okolju. Epidemiološke študije so pokazale povezavo med izpostavljenostjo nanodelcem iz zraka in vplivi na srčnodihalni in živčni sistem. V zadnjem času so se pojavili tudi novi materiali, ki vsebujejo nanodelce. Taki materiali imajo izboljšane lastnosti v primerjavi s »klasičnimi« materiali. Gre za materiale v elektroniki, gradbeništvu, biotehnologiji, živilski industriji, predmetih splošne uporabe itn. Izpostavljenost nanodelcem iz teh novih materialov lahko tudi predstavlja tveganje za zdravje.

Verjetnost za nastanek škodljivih posledic na zdravje pri znani oziroma predvideni izpostavljenosti (z vdihavanjem, z zaužitjem, skozi kožo) nanodelcem iz našega okolja presodimo z oceno tveganja. Vsaka ocena tveganja zahteva kakovostne informacije o identiteti in uporabi snovi, kateri smo izpostavljeni. Morajo biti poznani škodljivi učinki na zdravje, ki jih snov povzroča in varen referenčni odmerek (identifikacija in karakterizacija nevarnosti). Oceniti moramo izpostavljenost (ugotoviti velikost odmerka in trajanje izpostavljenosti), nato pa tveganje karakterizirati; kvantificirati pogostost in stopnjo škodljivih učinkov. Za oceno tveganja za zdravje zaradi izpostavljenosti nanodelcem iz novih materialov potrebujemo temeljito fizikalno-kemijsko karakterizacijo tako samega materiala, ki vsebuje nanodelce, kot materialov uporabljenih v študijah toksičnosti, ker različne fizikalno-kemijske lastnosti vplivajo na potencialne biološke učinke. Takšna karakterizacija vključuje sestavo in čistost materiala, velikost, obliko in strukturo sestavnih delcev, kemično sestavo in velikost površine, površinski naboj, kristalno obliko in fazo, stanje aglomeracije in/ali agregacije, kemijsko reaktivnost nanomateriala (in snovi na površini delcev), informacije o katalitični aktivnosti in potencialu tvorbe reaktivnih radikalov itd.

V prispevku predstavljamo primer ocene tveganja zaradi izpostavljenosti nanodelcem iz materialov v stiku z živili.

Health risk assessment due to exposure to nanoparticles from the environment

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Key words: nanoparticles, health risk assessment, exposure, physicochemical characterization, food contact materials

Nano-sized particles (1 to 100 nm) have been present in our environment since time immemorial. They occur during volcanic eruptions, sandstorms, soil erosion, fires. Humans also inadvertently produce them during various activities in the outdoor and the indoor environment. Epidemiological studies have shown an association between exposure to nanoparticles and effects on cardiorespiratory and nervous system. Recently, new materials containing nanoparticles have also been produced. Such materials have improved properties compared to "classical" materials. These are materials in electronics, construction, biotechnology, in the food industry, consumer products, etc. Exposure to nanoparticles from these new materials can also pose a health risk.

The probability of adverse health effects from known or predicted exposure (by inhalation, ingestion, through the skin) to nanoparticles from our environment is assessed through risk assessment. Each risk assessment requires quality information on the identity and use of the substance to which we are exposed. The adverse health effects of the substance and the safe reference dose (hazard identification and characterization), as well as exposure assessment, the dose and duration of exposure are required in order to enable risk characterization, i.e., quantification of adverse effects frequency and severity. To assess the health risks due to exposure to nanoparticles from new materials, we need a thorough physicochemical characterization of both the nanoparticle-containing material itself and the materials used in toxicity studies, because different physicochemical properties affect potential biological effects. Such characterisation may include material composition and purity, constituent particle size, shape and structure, surface chemical composition, surface area, surface charge, crystalline form and phase, agglomeration and/or aggregation state, chemical reactivity of the nanomaterial (including any surface coating), information on catalytic activity and reactive radical formation potential of the material etc.

In the presentation, we are describing an example of risk assessment due to exposure to nanoparticles from food contact materials.

Challenges in extracting information from peer-reviewed scientific articles to be used for risk assessment

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Keywords: food additives, re-evaluation, E 171, titanium dioxide

This presentation aims at providing an overview on the EFSA's work on the safety assessment of the food additive titanium dioxide (E 171)[1] as well as at elucidating the main challenges in identifying the scientific evidence to be used for the evaluation. According to Regulation (EC) No 1333/2008[2], all food additives permitted before 20 January 2009 should be subject to a new risk assessment by EFSA. Data gaps identified during the re-evaluation of food additives require a follow-up[3]. The risk management decision on whether a food additive and its uses/use levels remain permitted in the European Union will be taken based on EFSA's scientific opinions.

In order to gather all information available, the European Commission/EFSA launch calls for data to invite interested business operators to submit specific data. Information is complemented with data from peer-reviewed scientific articles. This implies to perform an extensive literature search and to establish an impartial and rigorous process to appraise the scientific evidence. The number of articles published for a specific topic depends on the public and scientific interest that encourages research in that area. In recent years, interest in nanomaterials has grown considerably and new knowledge on their characterisation and how to perform the safety assessment for nanomaterials or materials containing a fraction of nanoparticles, as E 171, is being developed.

The recent EFSA assessment on the safety of E 171 has requested an initial screening (by title and abstract) of nearly twelve thousand papers published in the last six years. Followed by the selection of the data for the assessment, that implied a screening of the studies for their relevance and an appraisal of their reliability (evaluation of the risk of bias). Analysing and integrating the evidence from the relevant and reliable studies allowed to draw conclusions on the safety assessment.

[1]EFSA FAF Panel (EFSA Panel on Food Additives and Flavourings), Younes M, Aquilina G, Castle L, Engel K-H, Fowler P, Frutos Fernandez MJ, Fürst P, Gundert-Remy U, Gürtler R, Husøy T et al., 2021. Scientific Opinion on the safety assessment of titanium dioxide (E171) as a food additive. EFSA Journal 2021;19(5):6585, 130 pp. https://doi.org/10.2903/j.efsa.2021.6585; [2]Commission Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives. OJ L 354, 31.12.2008, p. 16.; [3]https://ec.europa.eu/food/sites/food/files/safety/docs/fs_food-improvement agents_reeval_approach.pdf

Challenges in oral toxicity studies for the risk assessment of titanium dioxide in food

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Keywords: TiO_2, risk assessment, Adverse Outcome Pathways (AOPs), internal organ concentration, food additive E 171

Titanium dioxide (TiO_2) is a white pigment used as food colourant (food additive E171 in the EU). In addition, TiO_2 is used in medicinal products and toothpaste (partly swallowed by young children), leading to oral exposure. TiO_2 consists of particles which can have different physico-chemical properties. Recent studies reported adverse liver effects and intestinal tumor formation after oral exposure to TiO_2. Other oral toxicity studies, however, observed no such effects, despite prolonged exposure and/or high doses.

Aiming to better understand whether TiO_2 can induce such effects at conditions relevant for humans, we performed a review on these studies using Adverse Outcome Pathways (AOPs) to structure information. AOPs not only focus on the eventual clinical/histopathological observations, but also take earlier steps (key events) in consideration. In addition, the available information on organ concentrations of titanium (resulting TiO_2 exposure) from animal studies was compared to concentrations found in human postmortem organs.

The overview obtained using the AOP approach indicates that TiO_2 can trigger a number of key events in liver and intestine, such as the generation of reactive oxygen species, induction of oxidative stress and inflammation. TiO_2 seems to be able to exert these early effects in animal studies at titanium liver concentrations not much higher than the liver concentrations found in humans. This confirms earlier conclusions that adverse effects in humans cannot be excluded.

Diverging outcomes of animal toxicity studies could be explained by differences in dose, formulation and method of administration. At high doses, TiO_2 could agglomerate or aggregate, which could also occur during dispersing TiO_2 in the formulation given to animals. Also, methods of administering differ between studies, i.e. via oral gavage, the diet or drinking water. These aspects can alter uptake and subsequent effects in toxicity studies and recommendations are given to take such aspects into account.

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SIS EGIZ koordinira delovanje strateškega raziskovalnega inovacijskega partnerstva SRIP Zdravje - medicina, enega od stebrov izvajanja S4. S povezovanjem in mreženjem nastajajo nove priložnosti za organizacije, ki želijo izkoristiti razvojne priložnosti v sklopu projektov Strategije pametne specializacije Slovenije. Stičišče povezuje inovacijske akterje oz. raziskovalne skupine znotraj Slovenije med seboj in s partnerji v svetu, s ciljem doseganja prebojne kritične mase.

SIS EGIZ je pridobil certifikat Reference Site Slovenia pri evropskem inovacijskem partnerstvu za aktivno zdravo staranje EIP on AHA.