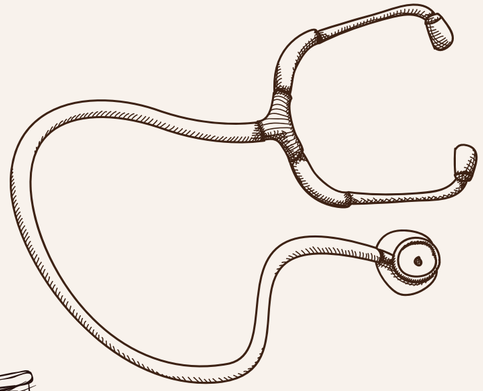
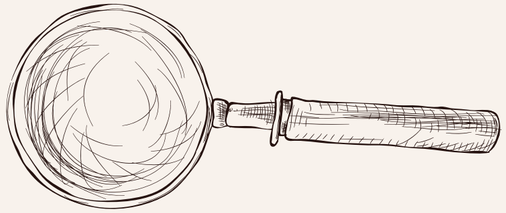
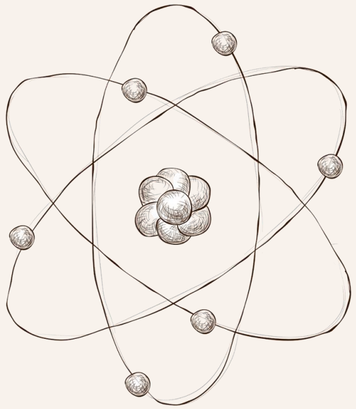


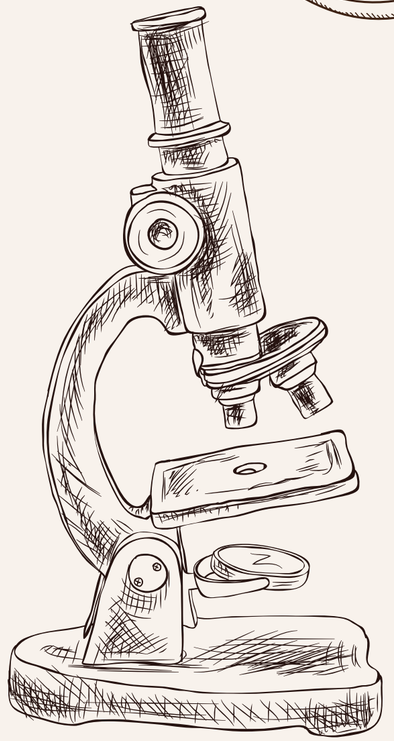


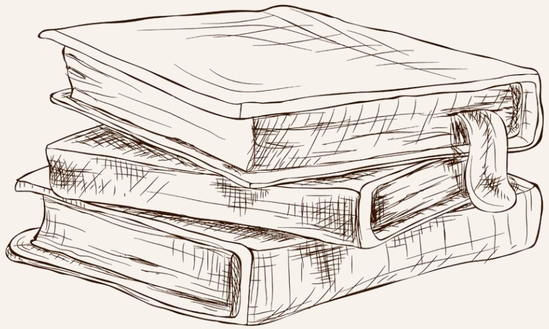
PARC Partnership FOR THE Assessment OF Risks FROM Chemicals



PREDSTAVITEV IZBRANIH NALOG V OKVIRU DP4

Manca Ahačič, Lucija Perharič





Naloge 4.1.3 – povezovanje izpostavljenosti in podatkov, povezanih z zdravjem

4.1.3.1a Izpeljava na humanem biomonitoringu temelječih smernih vrednosti (angl. “HBM Guidance Values”; HBM-GV)

4.1.3.3a/b/c Ugotavljanje povezanosti med izpostavljenostjo kemikalijam, zdravstvenimi izidi in biomarkerji učinka

Projekt 4.1.3.1a – Izpeljava HBM-GV

- HBM-GV za splošno populacijo in poklicno izpostavljene odrasle osebe: koncentracija kemikalije ali njenih presnovkov v človeških tekočinah ali tkivih, pri kateri glede na trenutno znanje ni tveganja za pojav negativnih učinkov za zdravje:
  - splošna populacija → dolgoročna izpostavljenost,
  - delavci → izpostavljenost preko celotne delovne dobe

- kemikalije brez praga učinka (genotoksične rakotvorne snovi) → HBM ekvivalenti izpostavljenosti za tveganje raka (angl. “HBM Exposure Equivalents for Cancer Risk”; HBM-EECR)

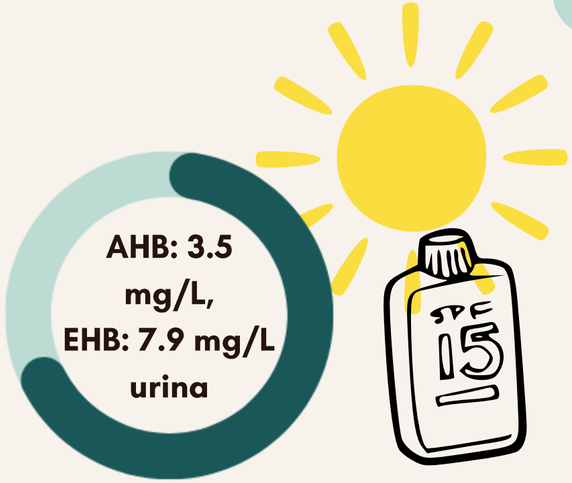
HBM-GV

obravnavane kemikalije (M1 - M36)

- ftalati z alternativami (DiNP, DiDP, DEP, DEHTP, DEHA), mešanice kemikalij!
- kovine:
  - Al: veliko različnih spojin in poti izpostavljenosti, januarja prvi osnutek poročila;
  - Cr VI: posodobitev trenutne mejne vrednosti, ki ni skladna z evropskimi cilji, posebej za delavce v procesih kromiranja in varilce,
  - Hg (M36),
  - As,
  - Ni,
- PFAS (v fazi določanja obsega dela),
- bisfenoli (A, S, F) obravnava v luči posodobljene vrednosti TDI s strani EFSA,
- dodaten pesticid po izbiri

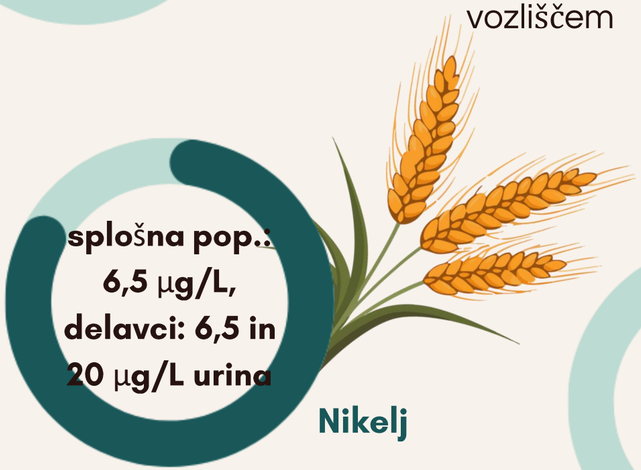
Cihalotrin:

- osnova za določitev HBM-GV za splošno populacijo = ADI 0.0012 mg/(kg tm/d) za γ-cihalotrin (EFSA 2014),
- poročilo pregledano znotraj skupine in oktobra posredovano nacionalnim vozliščem



Uvinul A Plus (DHHB):

- podlaga za opredelitev HBM-GV za splošno populacijo = NOAEL za razvojno toksičnost pri podganah,
- metabolita AHB in EHB**,
- HBM-GV za delavce v pripravi,
- poročilo pregledano znotraj skupine in nacionalnih vozlišč, slabši odziv



Nikelj

Benzofenon 3

- opredeljen kritični učinek: reprotoksičnost,
- endokrini potencial,
- HBM4EU: HBM-GV za splošno populacijo: 340 µg/g kreatinina

*metabolit cihalotrina: Cis-3-(2-kloro-3,3,3-trifluoroprop-1-enil)-2,2-dimetilciklopropankarboksilna kislina,
** 2-(4-amino-2-hidroksibenzoil) benzojska kislina (AHB) in 2-(4-(etilamino)-2-hidroksibenzoil) benzojska kislina (EHB)

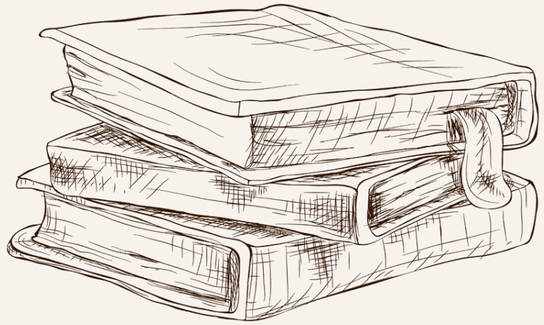
Nikelj

01 akutni in kronični toksični učinki pogojeni s kemijsko obliko, topnostjo in biodostopnostjo ter potjo izpostavljenosti (zaužitje, vdihavanje ali stik s kožo),

02 splošna populacija (z izjemo kadilcev) primarno izpostavljena preko uživanja živil in v manjši meri s pitjem vode, pri poklicno izpostavljenih skupinah prednjačita vdihavanje in stik s kožo

03 klasifikacija Mednarodne agencije za raziskovanje raka (angl. “International Agency for Research on Cancer”; IARC): nikljeve spojine - rakotvorna skupina 1, nikelj kot kovina in nikljeve zlitine - skupina 2B kot morda rakotvorne snovi za človeka

04 pojavljanje raka na pljučih, v nosnih in obnosnih votlinah le v primeru vdihavanja, trenutno ni na voljo raziskav, ki bi dokazale povezanost med pojavom rakavih sprememb in oralno izpostavljenostjo niklju

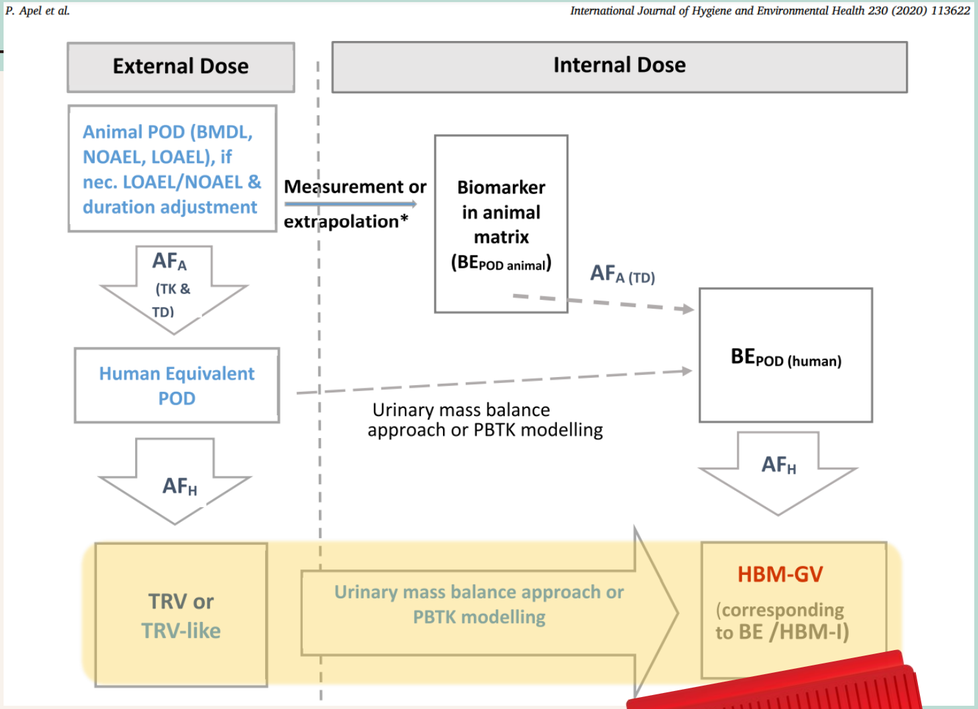


Izpeljava HBM-GV za splošno populacijo

- temelji na **reprotoksičnih učinkih**,

BMDL$_{10}$1.3 mg/kg tm/dan
varnostni faktor 100
TDI*: 13 µg/kg tm/dan,

- **EFSA 2020:**
  - **kronična oralna izpostavljenost**,
  - kritični učinek: višja incidenca izgube ploda pri podganah



- Izpeljava temelji na pristopu **masnega ravnotežja (angl. "Mass Balance Approach") v urinu**:
  - TRV ("Toxicological reference value"): toksikološka referenčna vrednost, npr. TDI,
  - Fue ("Urinary excretion fraction"): delež izločanja kemikalije s sečem,
  - "Daily urinary flow rate adjusted to the bw": diureza v 24 urah/kg tm

glede na nova priporočila nemške komisije za humani biomonitoring, pod okriljem UBA**, je vrednost dnevne diureze enaka za odrasle kot otroke = **30 mL/kg tm/dan**

- topnost
- način vnosa:

s hrano/na tešče):
0,7 % – 27 % v 3 dneh

*dopustni dnevni vnos,
**Nemška Zvezna agencija za okolje

Apel, P., Rousselle, C., Lange, R., Sissoko, F., Kolossa-Gehring, M., & Ougier, E. (2020). *Human biomonitoring initiative (HBM4EU) - Strategy to derive human biomonitoring guidance values (HBM-GVs) for health risk assessment. International Journal of Hygiene and Environmental Health, 230, 113622.* doi:10.1016/j.ijheh.2020.113622

01

$$HBM - GVGenPop = \frac{TRV * Fue(substance)}{Daily\ urinary\ flow\ rate\ adjusted\ to\ the\ bw}$$

$$= \frac{13\ \frac{\mu g}{kg}\frac{bw}{d} * 0.02}{0.03\frac{l}{kg}\frac{bw}{d}}$$

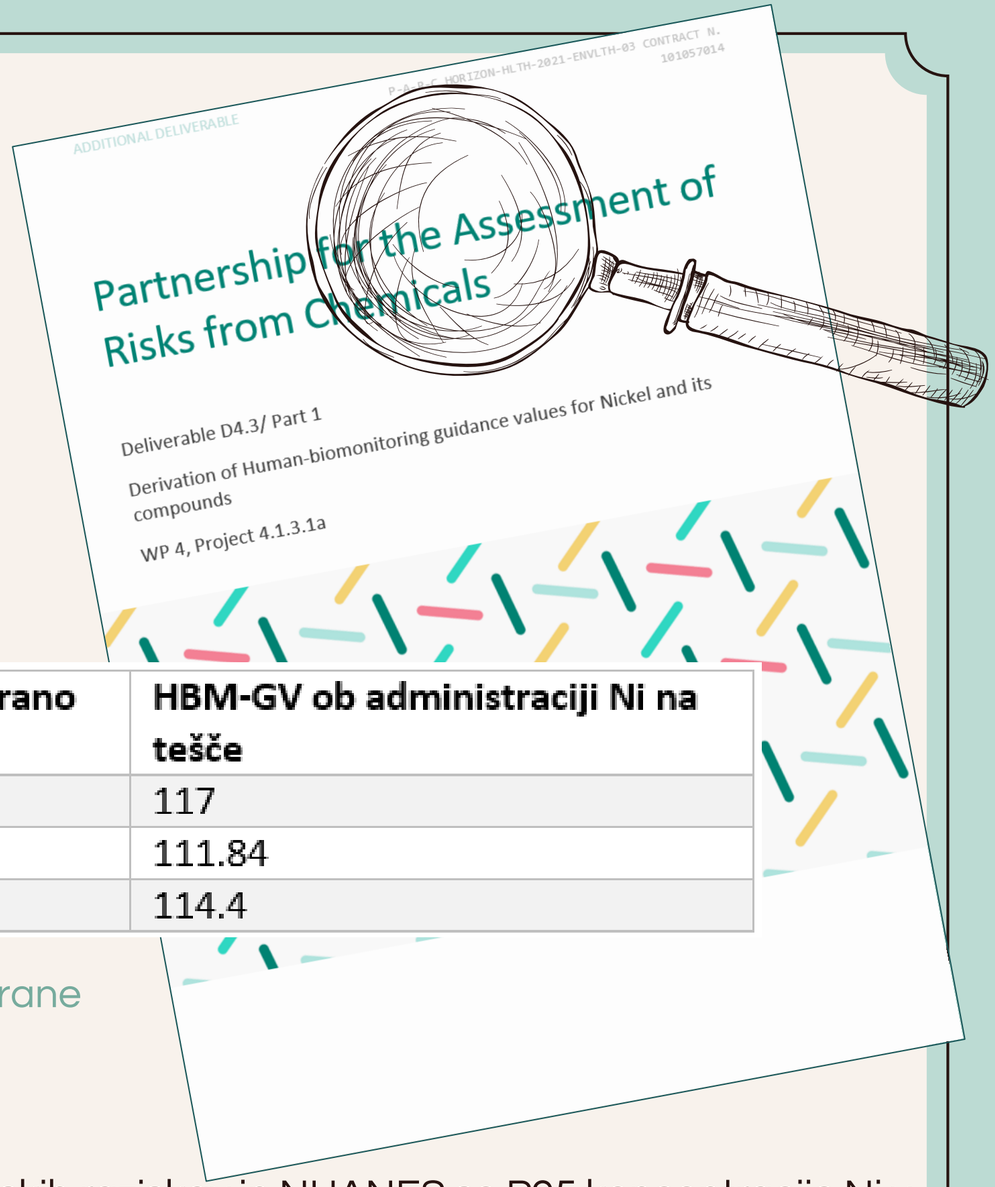
+

02

	HBM-GV ob zaužitju Ni s hrano	HBM-GV ob administraciji Ni na tešče
Sunderman et al. (1989)	3.03	117
Nielsen et al. (1999)	10.88	111.84
Povprečje obeh študij	6.93	114.4

=

izpostavljenost splošne populacije večinoma preko zaužitja hrane
→ povprečje rezultatov obeh študij zaokroženo navzdol



03

HBM-GV za splošno populacijo: **6,5 µg/L**

Glede na podatke evropskih raziskav in NHANES se P95 koncentracije Ni v urinu gibljejo v razponu od 4,3 do 6 µg/L v neonesnaženih regijah, medtem ko le-te v industrijsko onesnaženih območjih dosegajo celo 18 µg/L

Izpeljava HBM-GV za poklicno izpostavljeno populacijo

na podlagi pojavljanja raka nosnih in obnosnih votlin

01

- izpostavljenost predvsem preko **vdihavanja** → Ni kot **inhalatorni karcinogen**,
- RAC (ECHA) = Odbor za oceno tveganja Evropske agencije za kemikalije:
  - **OEL ("Occupational Exposure Limit"): omejitev poklicne izpostavljenosti = 0.03 mg/m³**
  - **zastavljena vrednost OEL** ščiti **tudi pred reprotoksičnimi učinki** (tako za $TDI_{EFSA\ 2015}$ 2.8 µg/kg tm/dan, kot tudi $TDI_{EFSA\ 2020}$ 13 µg/kg tm/dan):

$$\frac{13\ \frac{\mu g}{kg}\frac{tm}{d} * 60\ kg}{10\ m3} = 78\ \frac{\mu g}{m3} > 30\ \frac{\mu g}{m3}$$

- TDI = 13 µg/kg tm/dan,
- dnevni dihalni V za delavce (ECHA priporočila): 10 m³ (za 8-urno izpostavljenost)

Pretvorba izpostavljenosti z zaužitjem (TDI) → izpostavljenost preko vdihavanja

02

različne nikljeve spojine → razlike v topnosti in kinetičnih značilnosti → opredeljeni **2 HBM-GV**

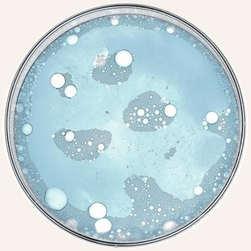
Vodotopne Ni spojine

grobi delci v zraku/zajetje širšega razpona velikosti zračnih delcev, boljši približek izpostavljenosti prahu

- pretvorba inhalabilne OEL v koncentracijo Ni spojin v urinu z uporabo enačb linearne regresije iz študij z najmočnejšo povezanostjo med koncentracijami Ni v zraku in urinu (r = 0,96),
- prevladovale študije delavcev v rafinerijah niklja in zaposlenih v procesih galvanizacije,
- razpon izračunanih koncentracij Ni v urinu, ki ustrezajo inhalabilni OEL: 20,5 – 111,3 µg/L

$HBM\text{-}GV_{delavci}$ = 20 µg/L

Slabo topne Ni spojine



- prevladovale študije poklicne izpostavljenosti med varjenjem nerjavnega jekla,
- razpon izračunanih koncentracij Ni v urinu, ki ustrezajo inhalabilni OEL: 4,70 µg/L – 13,5 µg/L

$HBM\text{-}GV_{delavci}$ = $HBM\text{-}GV_{spl.pop.}$ = 6,5 µg/L

- poklicna izpostavljenost = mešanica topnih in slabo topnih Ni spojin,
- ob neuporabi rokavic, je pomembna pot izpostavljenosti pri delavcih poleg vdihavanja tudi vnos “od rok do ust”,
- glavna pot izpostavljenosti splošne populacije je z uživanjem živil, pri delavcih vdihavanje → vnos niklja s hrano zmanjša delež izločanja topnih nikljevih spojin iz telesa → HBM-GV za delavce ščiti tudi pred nastankom reprotoksičnih učinkov

4.1.3 – Ugotavljanje povezanosti med izpostavljenostjo kemikalijam, zdravstvenimi izidi in biomarkerji učinka

4.1.3.3b **Biomarkerji učinka**

4.1.3.3c **Zdravstveni izidi**

prekrivanje vsebine
→ različna cilja

P4.1.3.3.a_Y1_ RoadmapLinking HBMhealth

Izvedba projekta v dveh korakih:

- vključitev meritev zdravstvenih izidov in biomarkerjev učinka v HBM raziskave preko standardiziranih anamnestičnih vprašalnikov (HES – "Health Examination Surveys"),
- izvedba študije izvedljivosti, v okviru katere se bo raziskalo možnosti ocenjevanja pretekle izpostavljenosti kemikalijam in določitve ravni biomarkerjev učinka na podlagi vzorcev, shranjenih v biobankah

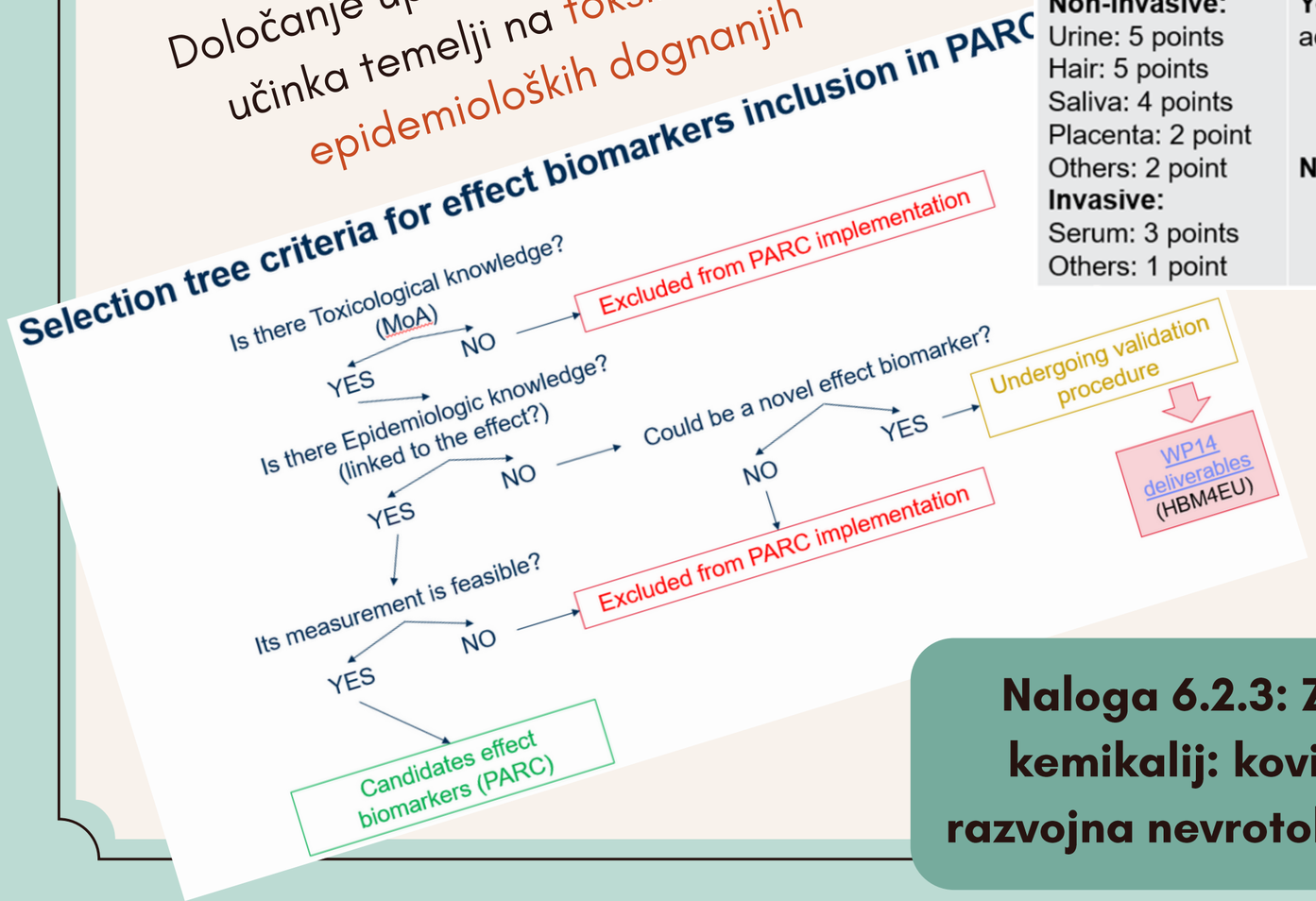
Biomarkerji učinka

Endpoint
Neurological system:
Neurodevelopment/-toxicity: **BDNF**; NF-L; PSD-95; SYP
Psychological stress: CRH; CORT; 11-HSD 1; GR; DNAmAge
Endocrine system:
Cardiometabolic health: **Kiss**, CRP, **LDL/HDL; TC; TG; Leptin; Adiponectin**; HOMA-IR; HbA1c; PPAR; AR; ER; AhR; SFLT-1; PDGF**;** IGF
Thyroid disease: **T3; T4; TSH; freeT3; freeT4**
Developmental toxicity; Puberty; Reproductive health: **Kiss; TT/FT; E2; LH; FSH; SHBG**; SFLT1; PDGF; Sperm quality; inhibinB; DHEA
Immune system:
Immune system: cortisol; C3; C3a; C4; CBC; Lymphocyte subsets; S1P; IgG, IgM
Hematoxicity: CBC; PT
Asthma and allergy; sensitization: IL-1,6; LTB4; TNF-alpha; IgE; IL-1beta; IFNgamma; IL8; eNO
Nephrotoxicity:
GGT; AST/ALT; ALP; Cr; NAG; Kim-1; alpha1-m; B2MG; NGAL; U-Ca; a-GST
Liver toxicity:
AST/ALT; ALP; Bilirubin; Albumin; PT; Transferrin
Carcinogenecity, oxidative stress and aging:
DNA damage and oxidative stress: TL; Micronucleus; Comet; γH2AX; DNA adducts; 8-OHDG; MDA; 8-isoprostane; GSH/GSSG; Retinol binding prot; MAPK; DNA methylation/demythylation **(BDNF; Kiss)**; CaMKB; Histones methylation; Chromosomal aberrations; sister chromatid exchange
Carcinogenecity: Micronucleus; **8-OHDG**; NSE; SCC; CYFRA-21-1; CA72-4; AFP; 3-nitrotyrosine; PSA; CC16; SP-D; Total plasma homocysteine
Aging: DNAmAge; TL; mDNA-CN; ERK

Biomarkerji učinka

Določanje uporabnosti biomarkerjev učinka temelji na toksikoloških in epidemioloških dognanjih

Score to select effect biomarkers as candidates for inclusion in PARC (**Max. 20 points**)				
Has the biomarker been assessed in human matrices?	Is there a plausible mechanism of action (MoA)?	Is an AOP reported for this effect	Has the biomarker been implemented in epidemiologic studies?	How would you define the feasibility, based on cost, efficacy, specificity, sensitivity and reliability of the effect biomarker
Non-invasive: Urine: 5 points Hair: 5 points Saliva: 4 points Placenta: 2 point Others: 2 point **Invasive:** Serum: 3 points Others: 1 point	**Yes:** report it and add 2 points **No:** 0 points	**Yes:** report it, provide the email link, and add 3 points **No:** 0 points	**Yes:** provide the DOI, and add 5 points **No:** 0 points	**Unsure:** Indicate your concern(s) and add 0 points **Low:** 0 points **Middle:** 2 points **High:** 5 points



Biomarkerji razvojne nevrotoksičnosti: 12 - 18 točk

Naloga 6.2.3: Zmesi kemikalij: kovine in razvojna nevrotoksičnost

Zdravstveni izidi

Toksikološko relevantne zvrsti arzena (TRA): As(III), As(V), MMA in DMA

- glede na podatke HBM4EU 37,4 % najstnikov preseglo biomonitorinški ekvivalent (BE) za nerakotvorne učinke (6.4 µg/L),
- pregled literature → glavne ugotovljene pomanjkljivosti:
  - pomanjkanje študij, ki so osredotočene na ugotavljanje učinkov izpostavljenosti As pri mladostnikih,
  - odsotna speciacija As, v večini študij je kemikalija navedena kot celotni As,
  - posredno ugotavljanje izpostavljenosti, preko meritev iz okolja

General survey		
Substances/Substances group	**Research interest**	**Target populations**
PFAS	Follow-up of HBM4EU: exceedance for the sum of 4PFAS in 14.26% of teenagers	All age groups (children, teenagers, adults)
Pesticides	Evaluate impact of regulation – Ban on chlorpyrifos and chlorpyrifos-methyl issued on 16/1/2020[2]	All age groups (children, teenagers, adults)
Metals	Study association with metals exposure: - Neurodevelopment outcome in children - Comparison with DEMOCOPHES Levels	All age groups (children, teenagers, adults)
Cadmium		Children, adults
Mercury		Children, adults
Bisphenols	BPS exceedance of HBM-GV in 11,2% of adults	All age groups (children, teenagers, adults)
Phthalates and substitutes	Higher levels observed in children > teenagers Reprotoxic effects Effect markers for sexual maturation in teenagers	Children, teenagers
Arsenic species	HBM4EU Arsenic (TRA) exceedance in 37.4% of teenagers	Teenagers
Organophosphate flame retardants	Follow-up of HBM4EU aligned studies: high prevalence and endocrine disrupting effects. The available epidemiological information on biomarkers of effect for OPFRs is limited. Translation of potential biomarkers from in vitro studies to human epidemiological research.	Children

Zdravstveni izidi (in potencialni biomarkerji učinka) v povezavi z izpostavljenostjo najstnikov TRA

Exposure biomarker	Linked health endpoint	Associated health measurements / Diagnosis	Available SOPs	Existing effect biomarkers	Proposed set of additional information
total As (tAs) in spot urine (males only)	neurobehavioral effects	CpGs	sequencing	**BDNF DNA methylation**	Gene polymorphisms - AS3MT, GSTO and folate metabolism genes, speciation of tAs, area of residence, annual family income, passive smoking; mothers: marital status, education, intelligence, employment, alcohol consumption; FFQ - monthly fish consumption, BMI
		neuropsychological test	questionnaire	Child Behavior Check List (CBCL/6–18)	
tAs in spot urine (and drinking water)	neurobehavioral effects	neuropsychological test	questionnaires	IQ - Ravens Standard Progressive Matrices (SPM), social competence (SC) - Texas Social Behavior Inventory (TSBI) Form - A // unadjusted for covariates	source and amount of water for cooking purposes (highly contaminated areas in Bangladesh; even if stopped drinking water from contaminated wells, still had continued using same water for cooking believing that the heat in the cooking process evaporates and destroys the As), FFQ (subsistence farming), SES (most families with poor SES and thus consuming highly As - contaminated tube well - water), housing type (corrugated tin walls/roofs - majority of households in low income stratum)
tAs in blood (co-exposure to As and Hg)	neuropsychological effects	11 int. recognized neuropsychological tests	questionnaires	Boston Naming Test (BNT); verbal (CVB) and executive function (EF)	source of drinking water, treatment method, fish consumption, source of fish, SES, BMI
iAs (arsenite, arsenate, MMA, DMA) in urine	cardiovascular diseases - atherogenesis	lipid and glucose metabolism	blood analysis	**lipid (total cholesterol (TC), TG, LDL HDL) and glucose (Glu levels, insulin resistance markers) metabolism markers**	obesity - BMI, BP, nutritional assessment
tAs, iAs, MMA, DMA in first morning urine (and tAs in drinking water)	cardiovascular diseases - atherosclerosis	anthropometrics (BMI), lipid and glucose metabolism - **glucose, TC, TG, HDL,** (LDL and VLDL calculated via Friedewald formula), atherogenic index (TC/HDL)	ultrasonography, blood analysis	carotid intima - media thickness (cIMT) as biomarker for subclinical atherosclerotic burden in conjunction with plasma asymmetric dimethylarginine (ADMA) as a predictor of cardiovascular disease risk and adhesion molecules (VCAM -1, sICAM - 1)	source of drinking water (Mexico - high concentrations of naturally occuring iAs in bedrock and consequently in underground and surface waters), marine food consumption, seconhand smoking exposure, detailed residential information, BMI, medical history (child allergies, medication,...)
tAs in urine and blood	cardiovascular diseases - hypertension	anthropometrics: height, weight, BMI, blood pressure	available	systolic blood pressure (SBP)	Adolescents' current and early childhood exposure to As positively associated with **SBP**. The associations were independent of other exposures, and were stronger in adolescents with higher **BMI**
no HBM (recall of lifetime well usage for drinking water - As level (<10, 10–50, >50 µg/L))	cardiovascular diseases	endothelial function	fingertip pulse amplitude tonometry	fingertip arterial pulsatile volume change and reactive hyperemia index (RHI) score	cardiovascular disease, source of drinking water (Bangladesh; an inverse relationship between lifetime reported well As concentration and endothelial function, as measured by RHI in adolescents), active/passive smoking

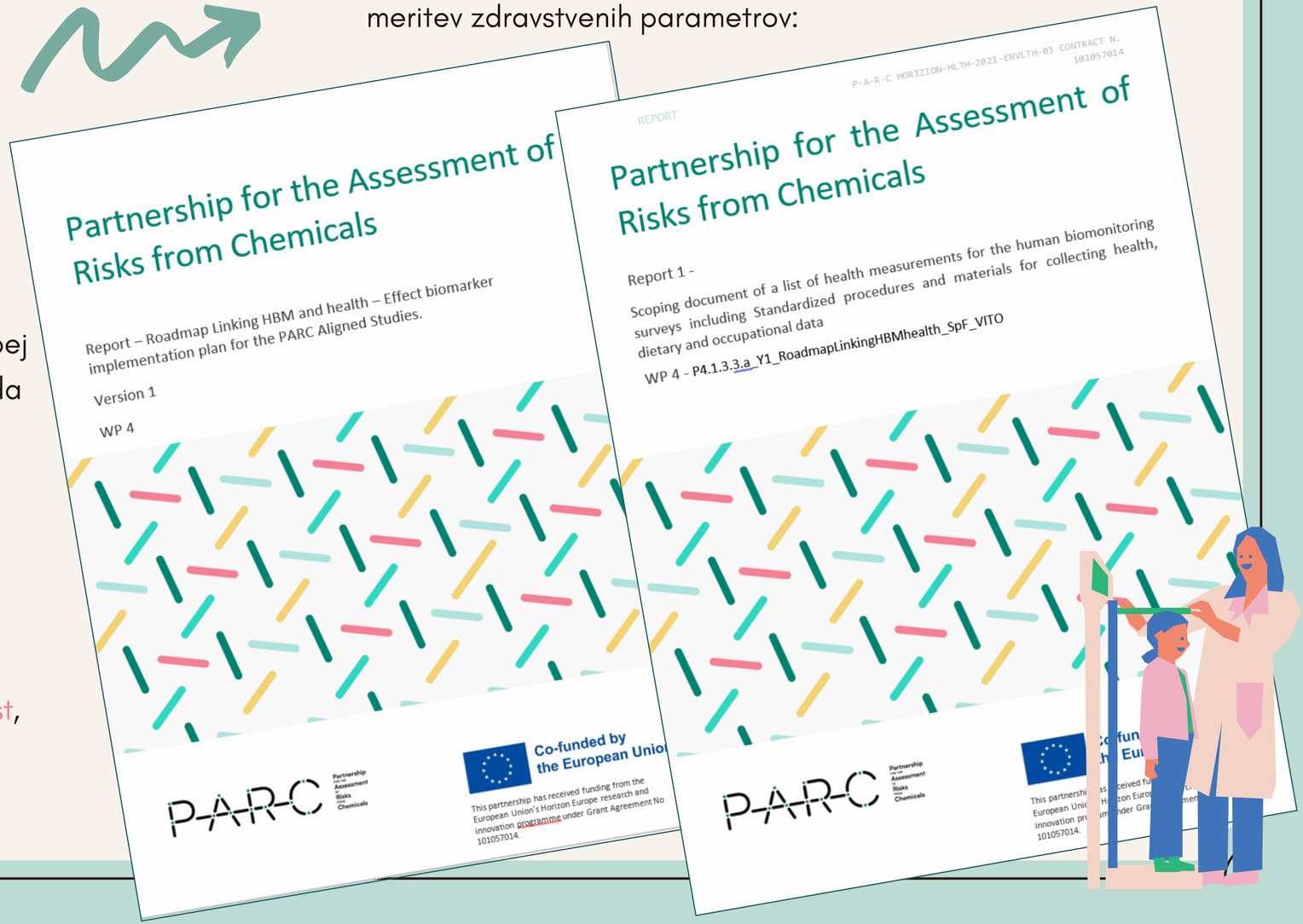
Exposure biomarker	Linked health endpoint	Associated health measurements / Diagnosis	Available SOPs	Existing effect biomarkers	Proposed set of additional information
tAs in urine	cardiovascular diseases, obesity	anthropometrics: height, weight, waist circumference (WC), BMI, BMI Z-score, SBP, DBP	blood analysis	**Fasting Blood Sugar (FBS), TC, TG, LDL, HDL** // cross-sectional study - no causal relationships explored	age (adolescents with higher levels of As than children), obesity - lipid profile, FBS
tAs in first morning urine (co-exposure to As and Pb)	carcinogenesis/ mutagenesis	**white blood cell count, (oxidative stress)**	real-time PCR	**leukocyte telomere length**	oxidative stress, area of residence (industrial area near an oil refinery, thermoelectric plant, an old fertilizer factory and important industrial corridor for automotive sector) – over-exploitation of the aquifer
iAs (arsenite, arsenate, MMA, DMA) in blood and urine	metabolic disorders/ obesity	anthropometrics	available	BMI (associations found only in females, not determined whether causal or not)	Bangladesh: source of drinking water, dietary habits (betel nut use), history of smoking, SES (education, land ownership), BMI, lean body mass (LBM) - computed separately for males and females, sex (BMI associated with As in female but not in male participants - further research needed to test whether the influence of adipose tissue in estrogen and choline synthesis is a major driver of the association between BMI and As methylation efficiency), plasma folate, plasma choline (adults)
iAs, MMA, DMA in blood plasma - fasting	metabolic disorders/ type 1 (and type 2) diabetes	anthropometrics: BMI, waist circumference; metabolic variables: estimated insulin resistance, autoantibodies,...	available	biomarkers of As metabolism: iAs%, MMA% DMA%, one - carbon metabolism biomarkers (folate, vitamin B12)	clinical diagnosis of type 1 and type 2 diabetes, plasma folate (type 1 diabetes was associated with lower plasma iAs% and higher MMA% and DMA%, in interaction analyses, the association between MMA% and type 1 diabetes was stronger for participants with higher folate levels), obesity status, BMI, ethnicity, age, sex, parental education level
tAs in urine, arsenobetaine and arsenocholine - speciation, iAs - subtraction	metabolic disorders/ nonalcoholic fatty liver disease (NAFLD)	anthropometrics: BMI; fasting blood samples - ALT; demographic variables - race/ethnicity	blood analysis	**ALT levels as a marker of liver damage**	ALT as a marker of liver dysfunction, BMI, race/ethnicity (positive association between urinary As exposure and risk of NAFLD among U.S. adolescents and adults that is highest among Mexican Americans and among those obese, regardless of race/ethnicity), annual household income
tAs in hair (co-exposure to 13 elements)		hematological evaluation, gene expression	RT - PCR	CYP450 (CYP1A1 - xenobiotic metabolism) and SOD (oxidative damage) mRNA levels	area of residence (industrial pollution)

Zdravstveni izidi (in potencialni biomarkerji učinka) v povezavi z izpostavljenostjo najstnikov TRA

Kriteriji za izbor zdr. izidov, meritev zdr, parametrov in biomarkerjev učinka

- relevantnost: vzročna povezanost izpostavljenosti kemikalijam z zdravstvenimi izidi,
- validacija (natančnost meritev pri ocenjevanju obravnavanih zdr. izidov) in zanesljivost (doslednost/ponovljivost meritev skozi čas, med različnimi raziskovalci in uporabljenimi inštrumenti),
- občutljivost (zaznavanje manjših sprememb, še posebej pri izpostavljenosti nizkim koncentracijam , ki se morda ne izrazijo v očitni klinični sliki),
- izvedljivost (razpoložljivost ustrezne opreme, laboratorijev, usposobljenega osebja, pripravljenost udeležencev za sodelovanje pri meritvah izbranih zdravstvenih parametrov in odvzemu določenih bioloških vzorcev),
- enostavnost zbiranja podatkov in etična neoporečnost,
- dostopnost referenčnih vrednosti

Tabele izbranih zdravstvenih izidov, biomarkerjev učinka in meritev zdravstvenih parametrov:



CHILDREN (6-11 years)	N studies	N samples	Country - matrix
Extended set of renal markers in urine (NAG (N-acetyl-β-D glucosaminidase), A1MG (α1-microglobulin), creatinine, albumin (albumin to crt ratio), Kim-1 (kidney injury molecule-1), RBP4 (Retinol-binding protein 4)	7	1700	Poland - MU; France - MU; Greece - MU; Spain - MU,SU; Luxembourg - MU; Germany - MU; Slovenia – MU*
8OHdG, 8-Oxo-2'-deoxyguanosine (urine)	6	1400	Poland - MU; Hungary - MU; Greece - MU; Spain - MU,SU; Luxembourg - MU; Slovenia – MU*

* Age Slovenia = 6-9

MU = morning urine; SU = spot urine

Vprašljiva uporaba biomarkerjev spolnega razvoja, leptina z adiponektinom in Kisspeptina z BDNF metilacijo:

- premajhen nabor vzorcev (delitev na moške in ženske),
- večinoma gre za naključne vzorce ("spot samples"),
- neujemanje starostnih razponov

Opredeljen nabor biomarkerjev učinka glede na zbrane podatke v sklopu delovnih skupin 4.1.3, točkovanja na podlagi določenih kvalitativnih in kvantitativnih kriterijev ter rezultatov 2 anket, poslanih lastnikom raziskav:

ADOLESCENTS (12-17 years)	N studies	N samples	Countries
Thyroid hormones in serum (FT3, FT4, T3, T4, TSH)	6	1750	France - FWB, FS; Greece - SWB, SS; Poland - SS; Belgium SS*, SWB; Germany - SS; Slovenia – SWB*, SS
Blood lipids in serum (Cholesterol, Triglycerides, HDL, LDL)	6	1750	France - FWB, FS; Greece - SWB, SS; Poland - SS; Belgium SS*, SWB; Germany - SS; Slovenia – SWB*, SS
Sexual development markers (LH, FSH, DHEAS, E2, TT, SHBG - note: Specific sampling conditions will apply for sexual development markers, see information leaflet)	3	750	Greece - SWB, SS; Poland - SS; Slovenia - SWB, SS*
Leptin + Adiponectin protein	3	750	Norway (SS, SWB)*; Greece - SWB, SS; Slovenia - SWB, SS*
Kisspeptin protein	4	1050	Greece - SWB, SS; Poland - SS; Belgium – SS*; Slovenia - SWB, SS*
BDNF protein	3	750	Poland - SS; Belgium – SS*; Slovenia - SWB, SS*
Kisspeptin + BDNF gene methylation	1	150	Slovenia - SWB, SS*

*Age: Belgium 14-16; Slovenia: 12-15; Norway 14-17

SWB = Spot whole blood; SS = Spot Serum
FWB = Fasting whole blood; FS = Fasting Serum

Vključitev izbranih meritev zdravstvenih parametrov, zdravstvenih izidov in biomarkerjev učinka v **anamnestične vprašalnike** HBM raziskav (HES)

Naloge 4.1.1.1 – Podporna gradiva in P4.1.1.2a_Y1_GenHBMSurvey

HBM II v okviru PARC

Design: *cross-sectional, stand alone HBM – possible connection with HES*

Implementation level: *national (9 regions)*

PARC General Survey: 3 out of 9 regions (1 urban, 1 rural, 1 potentially contaminated)

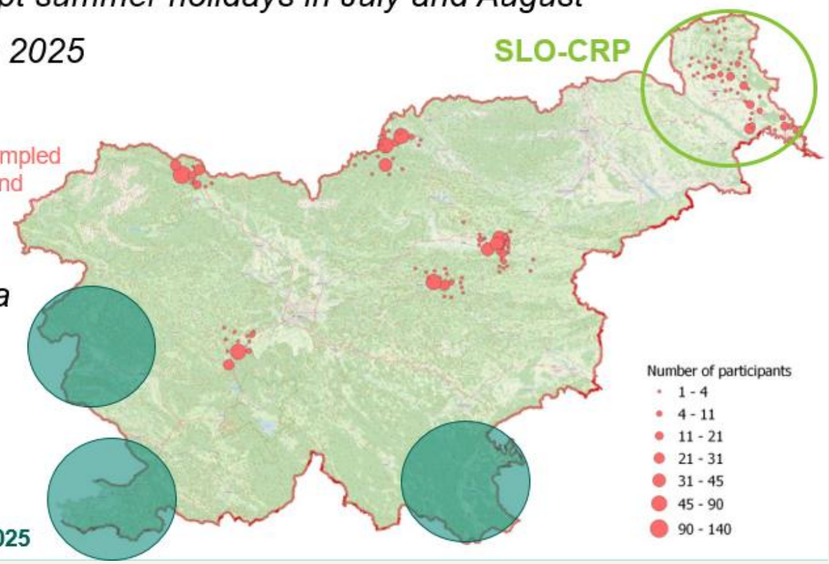
Timing of sampling: *started in 2018, across all seasons except summer holidays in July and August*

PARC General Survey: 2023 (autumn) – 2025

Age groups: *6–9 years (children)*
12–15 years (adolescents)

Sample size: *100 children and 100 adolescents per study area*
→ 300 children and 300 adolescents

Recruitment strategy: *parents with children of chosen age range invited **through schools** in the selected study areas*



Planned for 2023 (autumn) - 2025

Vir: Predstavitev v okviru DP4, 10.5.2023, Bruseljj; Janja Snoj Tratnik, Manca Ahačič

PARC Partnership FOR THE Assessment OF Risks FROM Chemicals

Hvala za pozornost!