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Epigenetic analyses and endocrine disruption: applicability in risk assessment

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Environmental Epigenetics Group Leader
Department of Integrative Biology,
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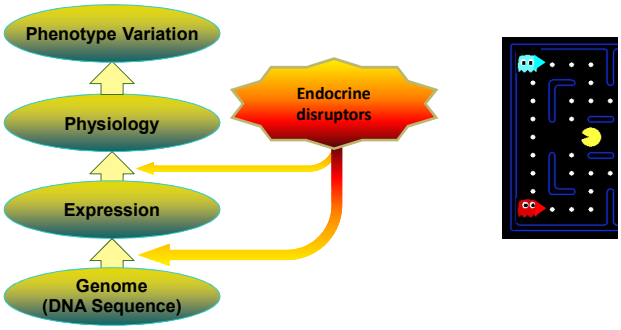
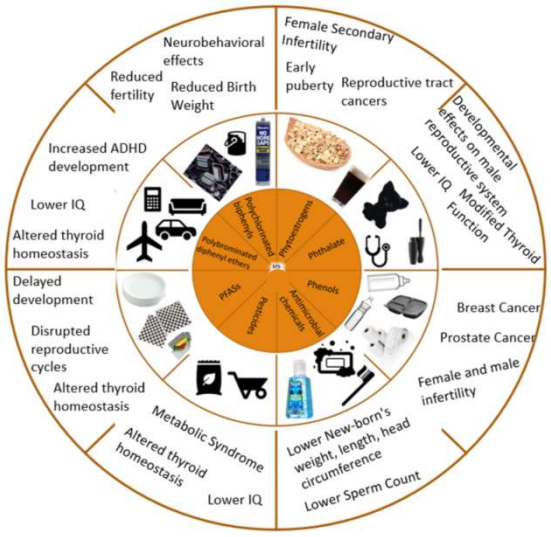


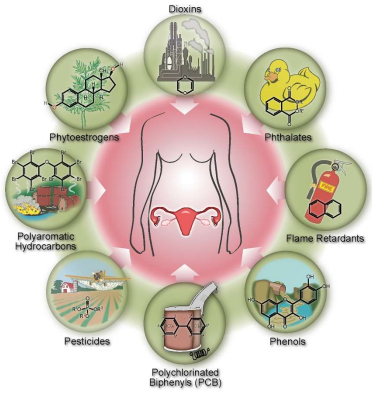
Endocrine Disruptors (WHO 2002 definition): "An exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny , or (sub) populations"

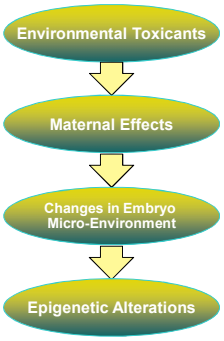
Known effects of Endocrine Disruptors



From: Polina Lizunkova

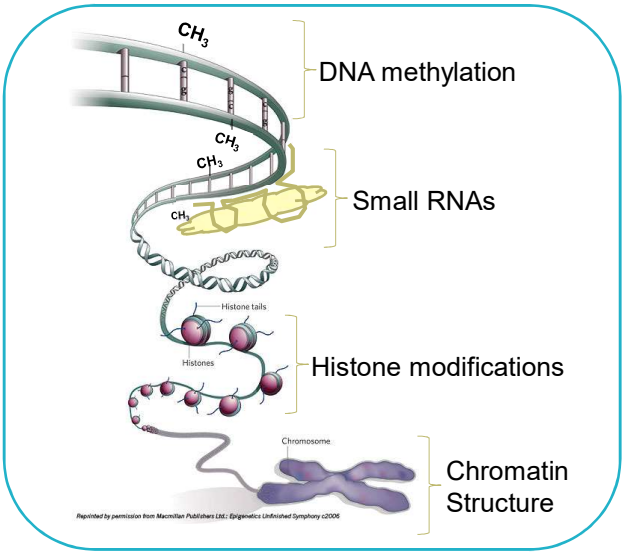
Endocrine Disrutptors can Influence Early Development



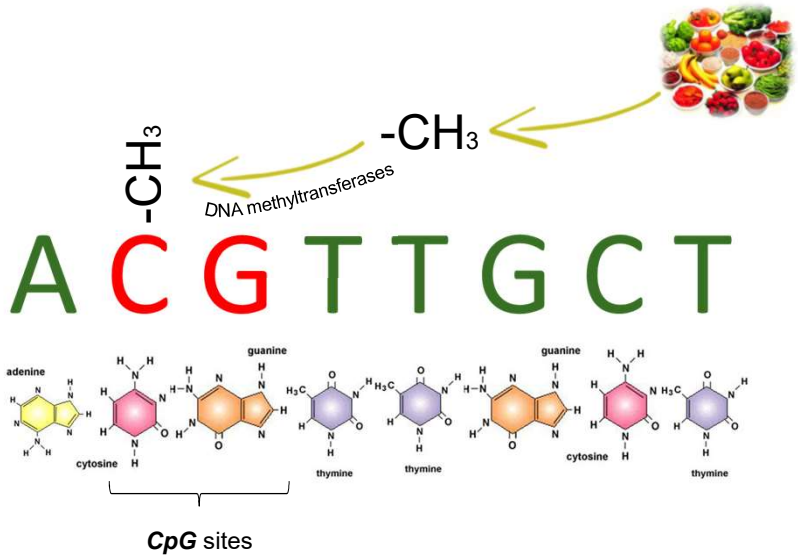


Epigenetics

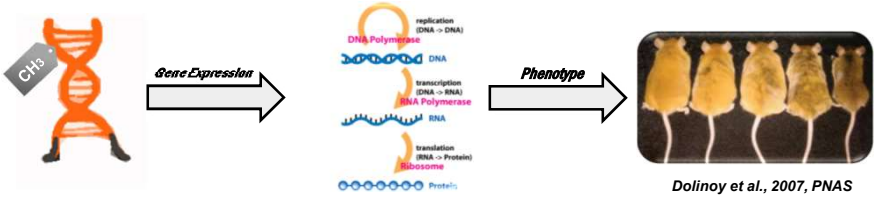
Accessory chemical modifications on the DNA or on proteins that pack the DNA



DNA methylation: an epigenetic mechanism

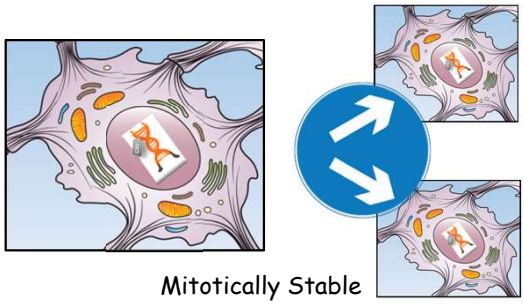


Epigenetic changes regulate gene expression….

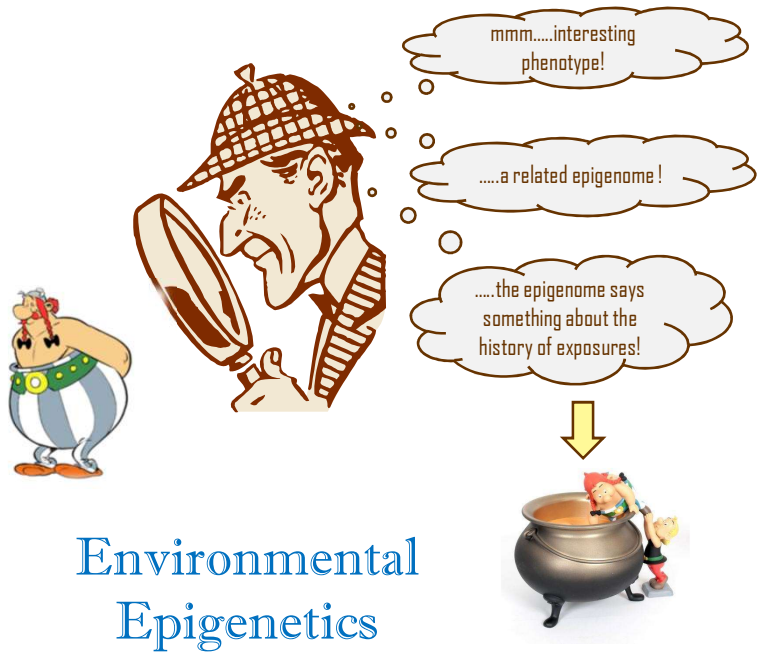


Dolinoy et al., 2007, PNAS

….and can survive cell division



Mitotically Stable



Environmental Epigenetics

Examples of epigenetic markers of exposure in humans

Peripheral blood

ARTICLE

https://doi.org/10.1038/s41467-021-22752-6 OPEN

Epigenome-wide association meta-analysis of DNA methylation with coffee and tea consumption

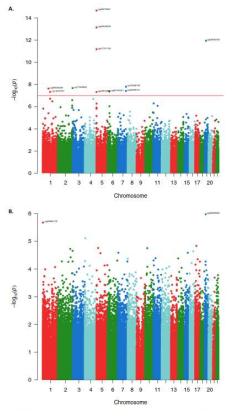
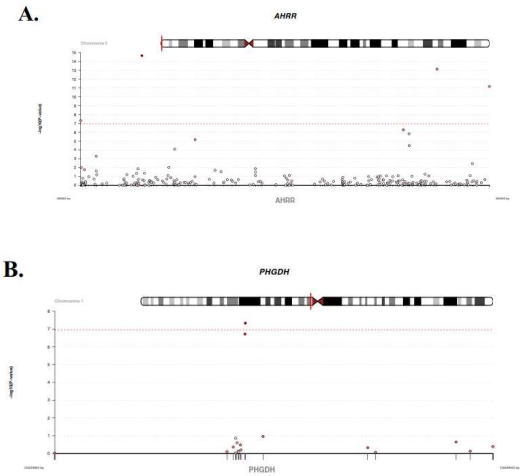


Fig. 2 Epigenome-wide association study Manhattan plots for coffee and tea consumption. The plots depict the results of EWAS fixed-effects inverse-variance meta-analysis with the overall sample for coffee (**A**) ($n = 15,789$) and tea (**B**) consumption ($n = 15,069$) in the fully adjusted model. Each dot corresponds to a single CpG site plotted as the negative logarithm of the p-value ($-\log(p\text{-value})$ (*y*-axis)) against the genomic position of the CpG site (*x*-axis). The red line indicates the Bonferroni adjusted threshold at epigenome-wide significance p-value of 1.1×10^{-7} (0.05/450,000).



Peripheral blood

International Journal of Epidemiology, 2018, 1120–1130
doi: 10.1093/ije/dyy091
Advance Access Publication Date: 31 May 2018
Original article

Tobacco

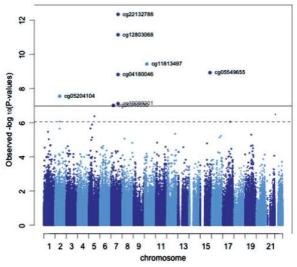
DNA methylation as a marker for prenatal smoke exposure in adults

Rebecca C Richmond,* Matthew Suderman, Ryan Langdon, Caroline L Relton† and George Davey Smith†

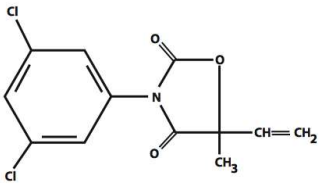
Table 2. DNA methylation changes associated with prenatal smoke exposure in ALSPAC women (Time Point 1)

CpG site	Chromosome	Gene region	Position	Basic model ($N = 754^a$)				Adjusted model[b] ($N = 752$)			
				Effect size	Standard error	*P*-value	FDR	Effect size	Standard error	*P*-value	FDR
cg22132788	7	*MYO1G*	45002486	0.062	0.008	1.70E-13	8.26E-08	0.058	0.008	9.77E-13	4.75E-07
cg12803068	7	*MYO1G*	45002919	0.111	0.015	9.82E-13	2.38E-07	0.097	0.014	1.71E-11	4.16E-06
cg11813497	10	*FRMD4A*	14372879	0.038	0.006	1.25E-10	2.02E-05	0.036	0.006	4.85E-10	7.85E-05
cg04180046	7	*MYO1G*	45002736	0.041	0.006	2.53E-10	3.07E-05	0.037	0.006	3.43E-09	3.33E-04
cg05549655	15	*CYP1A1*	75019143	0.007	0.001	1.21E-08	0.001	0.007	0.001	8.82E-10	1.07E-04
cg25949550	7	*CNTNAP2*	145814306	−0.005	0.001	1.48E-08	0.001	−0.004	0.001	2.41E-07	0.015
cg19089201	7	*MYO1G*	45002287	0.038	0.007	1.75E-08	0.001	0.034	0.007	1.88E-07	0.013
cg05204104	2	*ARL4C*	235403141	0.023	0.004	2.30E-08	0.001	0.023	0.004	4.12E-08	0.003
cg17924476	5	*AHRR*	323794	0.045	0.008	6.24E-08	0.003	0.040	0.008	5.33E-07	0.029
cg11429111	5	*TIFAB*	134813329	0.022	0.004	2.62E-07	0.013	0.019	0.004	2.90E-06	0.108
cg08241939	1	*MDM4*	204700816	0.022	0.004	5.04E-07	0.022	0.019	0.004	3.40E-06	0.110
cg11641006	2	*AX748264*	235213874	0.040	0.008	5.62E-07	0.023	0.029	0.006	1.27E-06	0.051
cg15016771	2	*ARL4C*	235403218	0.008	0.002	1.01E-06	0.036	0.007	0.002	3.35E-06	0.110
cg22807681	5	*DRD1*	174622933	0.023	0.005	1.04E-06	0.036	0.023	0.005	1.02E-06	0.045
cg26681628	16	*FTO*	54210550	0.037	0.008	1.27E-06	0.041	0.029	0.006	8.94E-06	0.193

Effect size = difference in methylation level (beta) between adult offspring of smokers and non-smokers in pregnancy.
Entries in bold represent sites that surpassed the Bonferroni threshold.
[a]$N = 216$ smoked during pregnancy, $N = 538$ no smoking during pregnancy.



Vinclozolin (Agricultural fungicide)



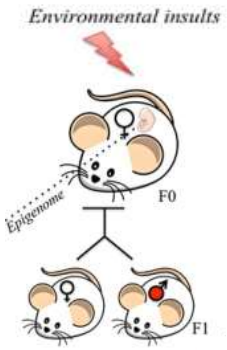
•Systemic fungicide (e.g. Wine Industry)

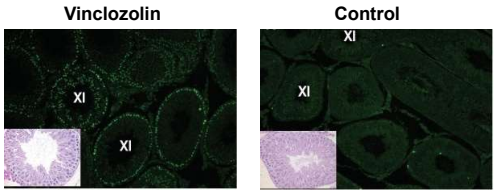
•Two metabolites: Butenoic acid and enanilide

• Vinclozolin and metabolites are anti-androgenic

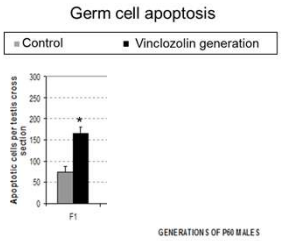
•Late embryonic/early postnatal exposure causes abnormal reproductive tract development and gonadal function

Transgenerational Epigenetic Inheritance



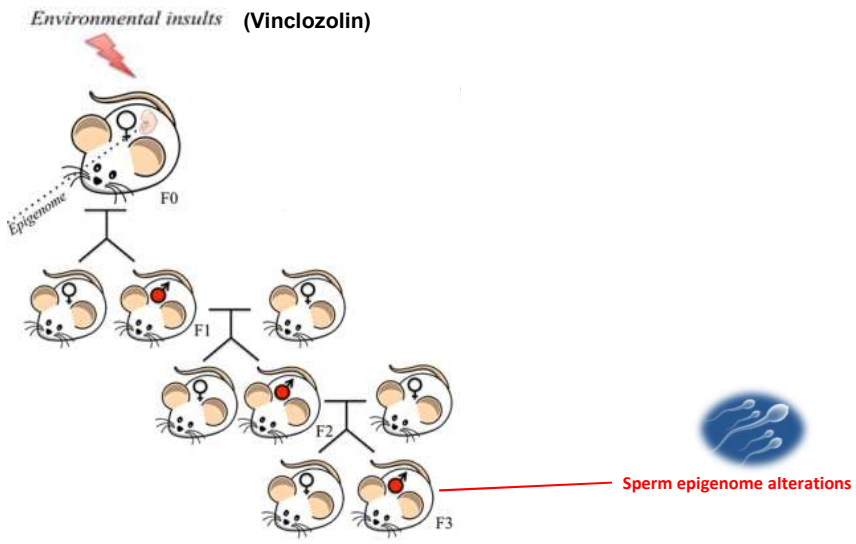


TUNEL assay



Uzumcu et al., 2004, Reprod Tox

Herencia epigenética transgeneracional

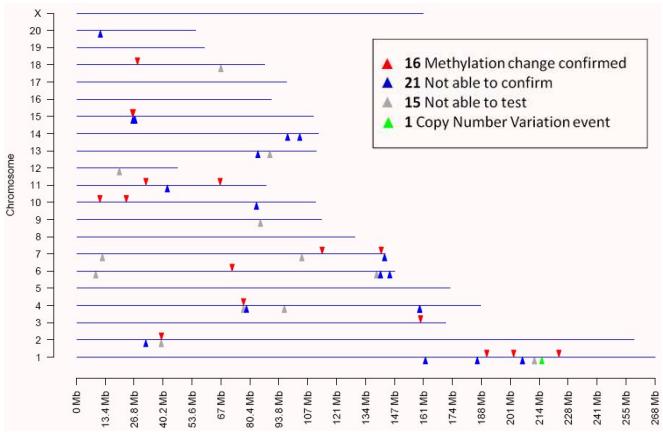


Epigenetic Transgenerational Actions of Vinclozolin on Promoter Regions of the Sperm Epigenome

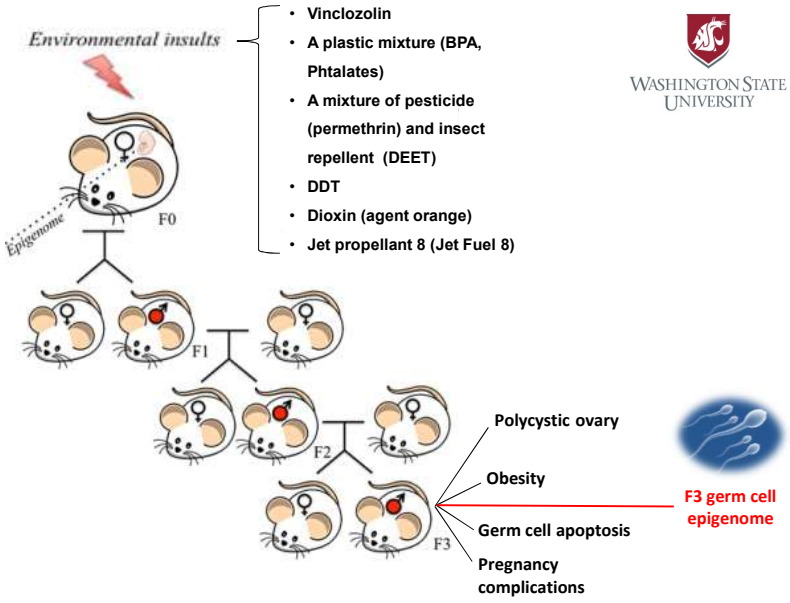
Carlos Guerrero-Bosagna, Matthew Settles, Ben Lucker, Michael K. Skinner*

PLoS ONE | September 2010 | Volume 5 | Issue 9 | e13100

52 Methylation Changes (48 promoters) in the sperm DNA of male rats 3 generations after a developmental exposure



Transgenerational Epigenetic Inheritance

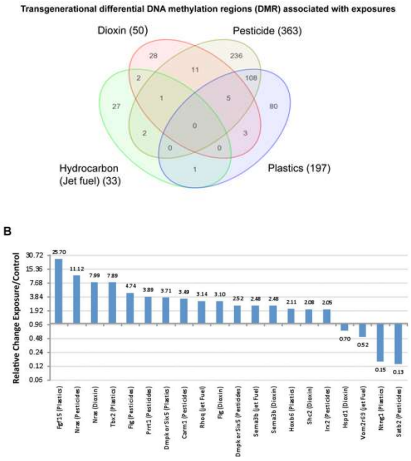


WASHINGTON STATE UNIVERSITY

Transgenerational Actions of Environmental Compounds on Reproductive Disease and Identification of Epigenetic Biomarkers of Ancestral Exposures

Mohan Manikkam, Carlos Guerrero-Bosagna, Rebecca Tracey, Md. M. Haque, Michael K. Skinner*

PLoS ONE | February 2012 | Volume 7 | Issue 2 | e31901



Epigenetic biomarkers of exposure in hazard assessment

Science of the Total Environment 773 (2021) 144830

Contents lists available at ScienceDirect

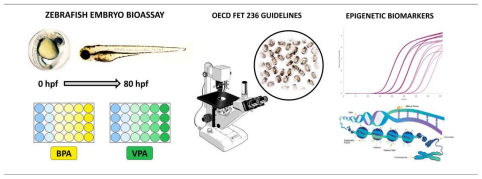
Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Epigenetic biomarkers as tools for chemical hazard assessment: Gene expression profiling using the model *Danio rerio*

Tiago Torres [a,b], Raquel Ruivo [a], Miguel Machado Santos [a,b,*]

GRAPHICAL ABSTRACT



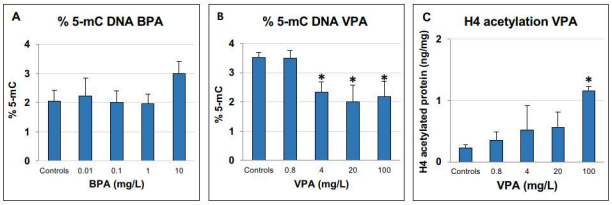


Fig. 1. Global DNA methylation and global H4 histone acetylation of *D. rerio* embryos exposed to different concentrations of BPA (A) and VPA (B and C) at 80hpf. Data are expressed as mean ± SE ($n = 5$). Significantly different results from controls ($p < 0.05$) are marked with a symbol (*). One-way-ANOVA (A and C) or Kruskal-Wallis Test (B).

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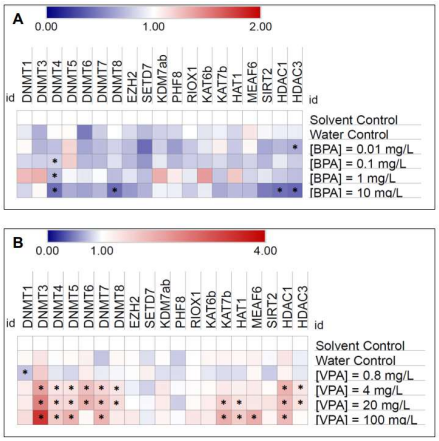


Environment International 144 (2020) 106020

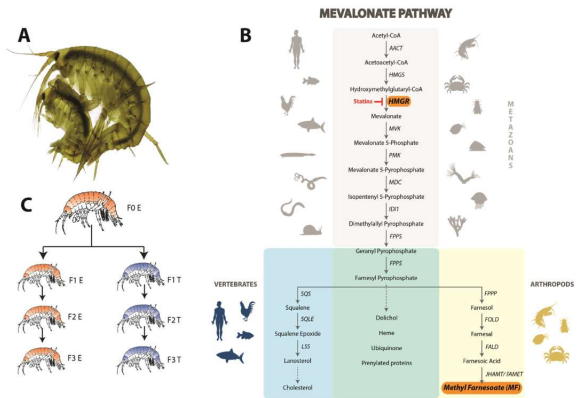
Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Transgenerational inheritance of chemical-induced signature: A case study with simvastatin

T. Neuparth[b,c], A.M. Machado[a,b], R. Montes[c], R. Rodil[c], S. Barros[a], N. Alves[a], R. Ruivo[a], L. Filipe C. Castro[b,d], J.B. Quintana[c], M.M. Santos[a,b,*]



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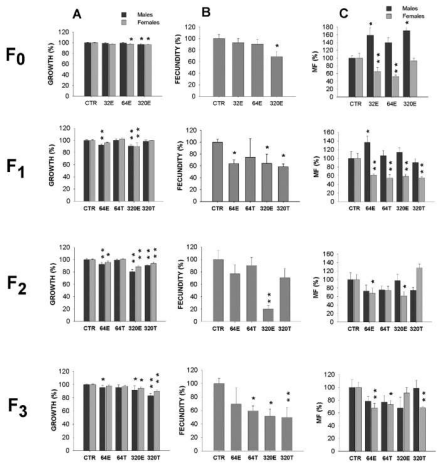


Ecotoxicology and Environmental Safety 209 (2021) 111849

Contents lists available at ScienceDirect

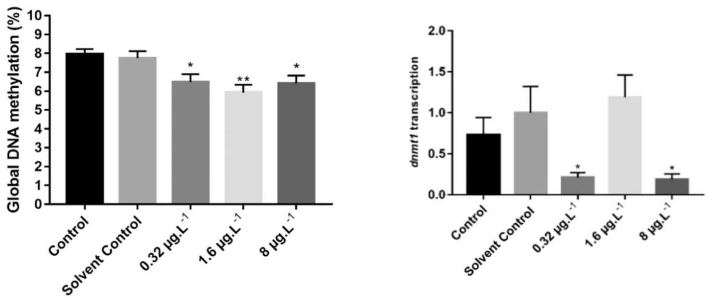
Ecotoxicology and Environmental Safety

journal homepage: www.elsevier.com/locate/ecoenv

Research paper

The anti-lipidemic drug simvastatin modifies epigenetic biomarkers in the amphipod *Gammarus locusta*

Nélson Alves[a,b], Teresa Neuparth[a,*], Susana Barros[a], Miguel M. Santos[a,b,**]



Epigenetic tools may fill gaps in risk assessment

- Chemical risk assessment currently involves hazard identification, dose-response assessment, exposure assessment, and risk characterization
- Although current guidelines include multigenerational effects of environmental pollutants, these are NOT integrated in hazard and risk assessment frameworks (Neuparth et al, 2020).
- Biomarkers of exposure for risk assessment analyses can indicate both life-long and transgenerational effects, as well as developmental and/or ancestral exposures

The Environmental Epigenetics Group

UPPSALA UNIVERSITET

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- Luis Coutinho, USP, Brazil
- Frederique Pitel, INRA, France,
- Brynn Voy, U Tennessee, USA
- Gina Galli, Manchester University, UK
- Per Jensen, Linköping University, Sweden

Current funding

Vetenskapsrådet

FORMAS

HORIZON 2020

GERONIMO

USDA United States Department of Agriculture

FNSNF Swiss National Science Foundation