

Report from

COST-Action No.15129:

DiMoPEx (Diagnosis, Monitoring, Prevention of Exposure Related Non-Communicable Diseases)

DiMoPEx



COST Action 15129

Work Group (WG) 5

Genotoxicity and Susceptibility

WG Leader: Dr. Nancy B Hopf

WG Expert Support:

Prof. Dr. Claudia Bolognesi

Assoc. Prof. Dr. Heidi Schwarzenbach

Prof. Dr. Fiorella Belpoggi

Dr. med. Daniele Mandrioli



COST is supported by
the EU Framework Programme
Horizon 2020



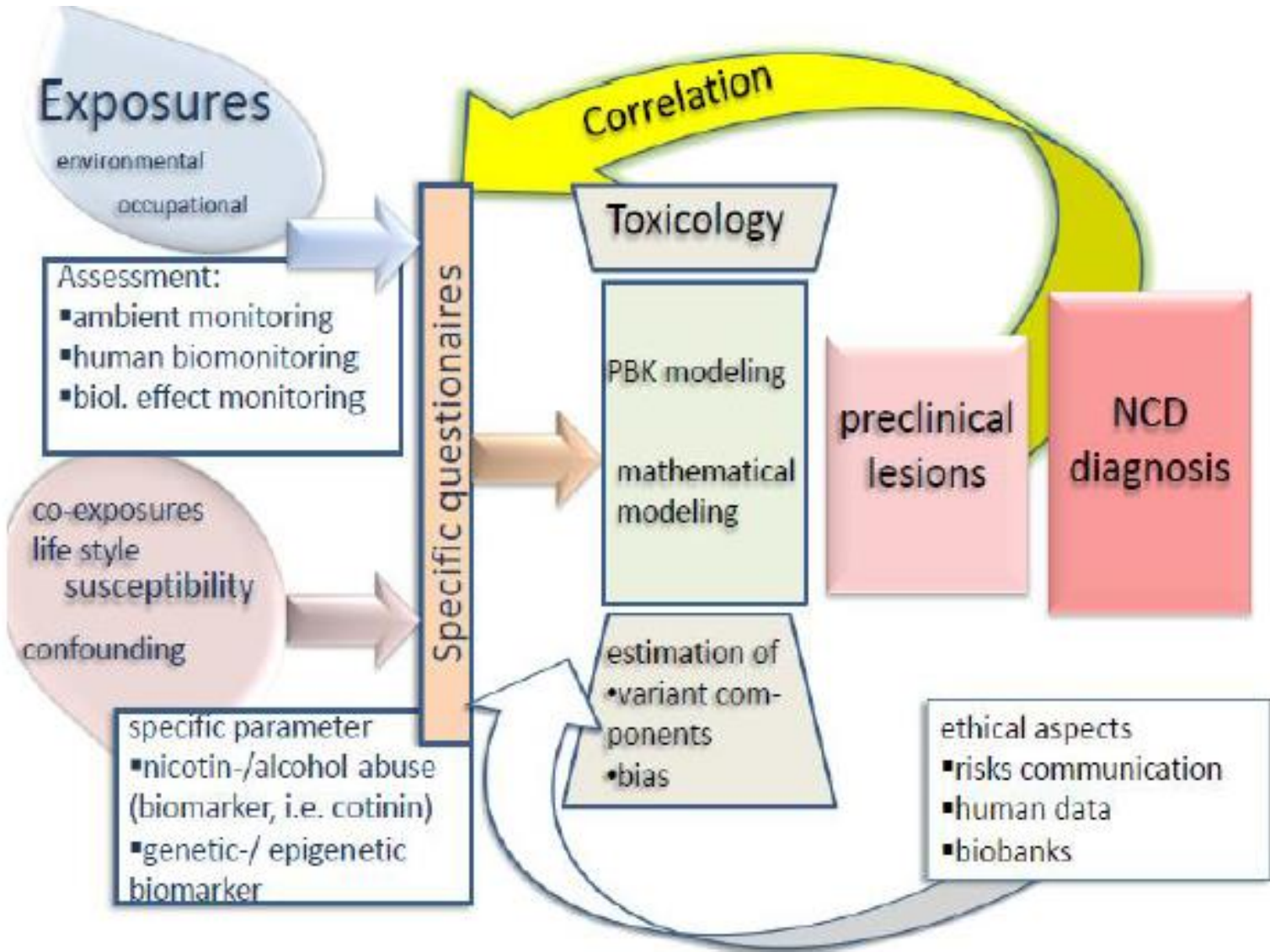
Aims

- identify determinants of prevalence and morbidity of diseases and of developing promising preventive intervention strategies
- to establish quantitative relationships between exposures to toxic hazards and the associated risks of the diseases

Generate risk assessment and prevention models to improve health and safety in Europe for the general public, and more specifically for workers, and for consumers



Focus on BIOMARKERS





Working Group 5

Goals

- Creation of a **network of laboratories** involved in the application of genotoxicity and epigenetic biomarkers. (CB MN training, FB DimoPEX conf)
- Standardization of the procedure for the application of the selected genotoxicity/epigenetic biomarkers
- Intercalibration exercises on specific biomarkers applied in multiple labs. (CB MN training)
- Identification of specific biomarkers of cancer in the DiMoPEX WG 5 (ongoing...)
- Evaluation of potential use of genotoxicity/epigenetic biomarkers in evaluation of risk assessment of chemicals. (NBH and CB meta-analysis)



Creation of a network of laboratories

- Training courses
- Exchange of protocols/guidelines expertise:
 - ✓ Criteria of scoring
 - ✓ Automated methods
 - ✓ Analysis of the data
 - ✓ Interpretation of the results
- Implementation of the *in vitro*/*in vivo* models



***In vitro* Evaluation of the Genotoxic Properties of Pencycuron, a Commonly Used Phenylurea Fungicide, by the Cytokinesis-Block Micronucleus (CBMN) Assay**

Karoly **Nagy**, Balazs Adam

University of Debrecen, Faculty of Public Health, Department of Preventive Medicine, Debrecen, Hungary

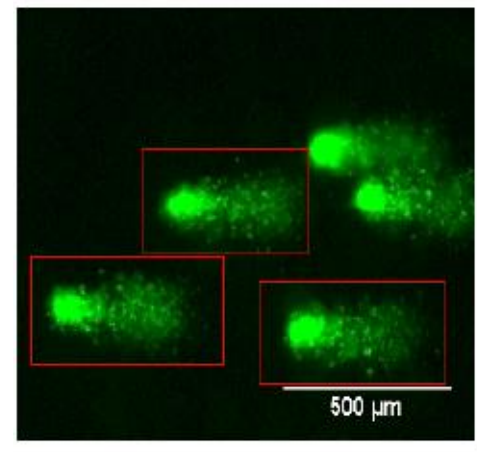
Claudia Bolognesi

Ospedale Policlinico San Martino IRCCS, Environmental Carcinogenesis Unit, Genoa, Italy



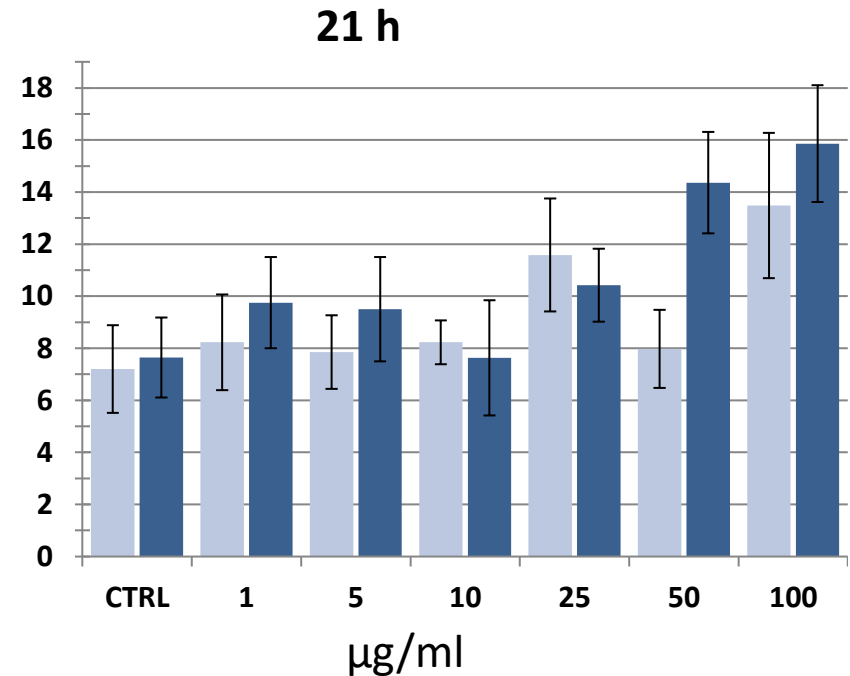
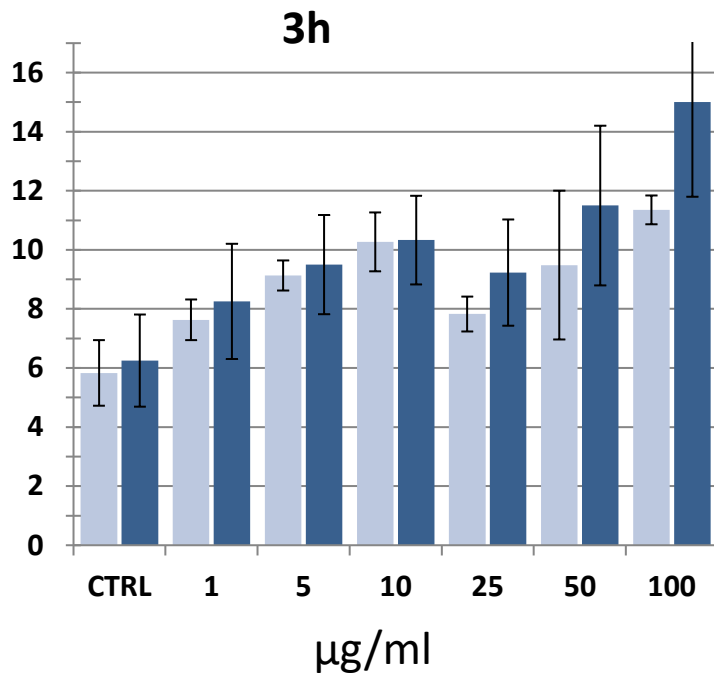
In vitro mammalian cell MN test (OECD guideline 487, 2010)

in the basic battery of tests to screen new chemical and physical agents for genotoxicity





Frequency of MNBN cells/1000 cells induced by exposure to different concentrations of pencycuron in human peripheral lymphocytes and HepG2 cell line



Results: provides some indication on a possible genotoxic effect of pencycuron as observed *in vitro* in two different human cell types in two laboratories.



In vivo micronucleus assay in bone marrow of Sprague-Dawley rats

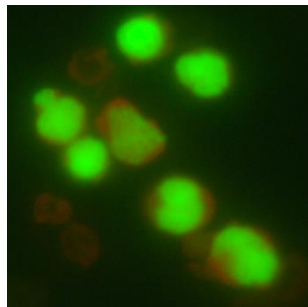
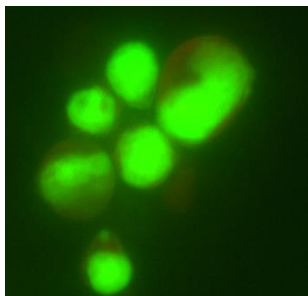
Pilot study on glyphosate/Roundup toxicity

Environmental Carcinogenesis Unit, Ospedale Policlinico San Martino, Genova, Italy

Ramazzini Institute, Cesare Maltoni Cancer Research Centre, Bentivoglio, Bologna, Italy

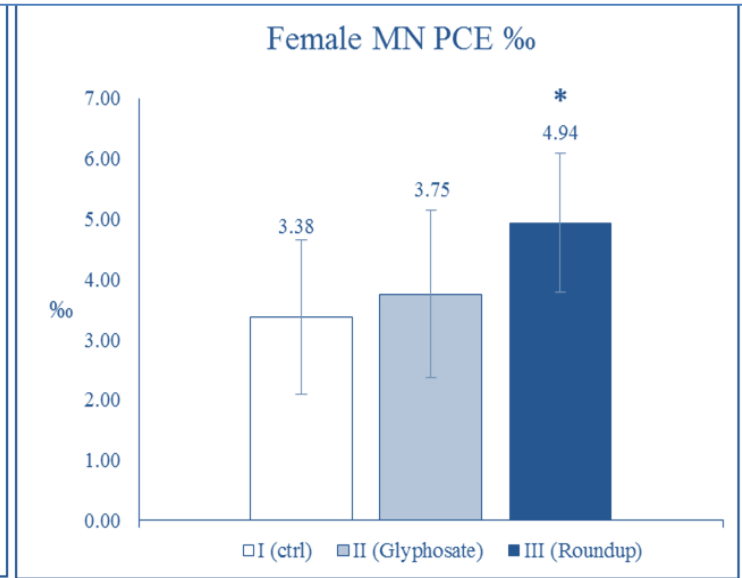
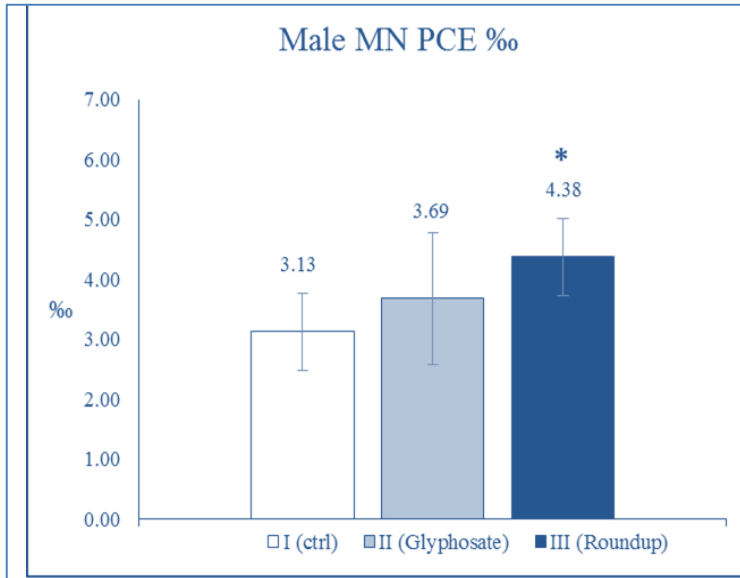


treated from the embryonic life up 120 PND at the US ADI (1.75 mg/kg/day).

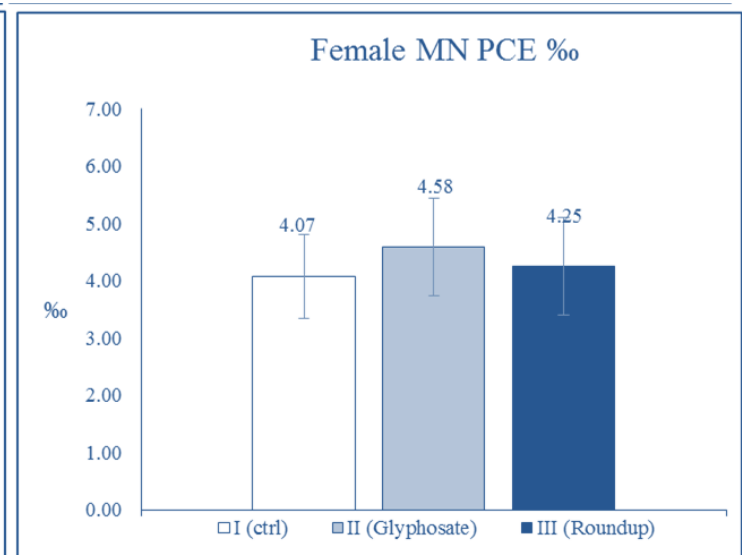
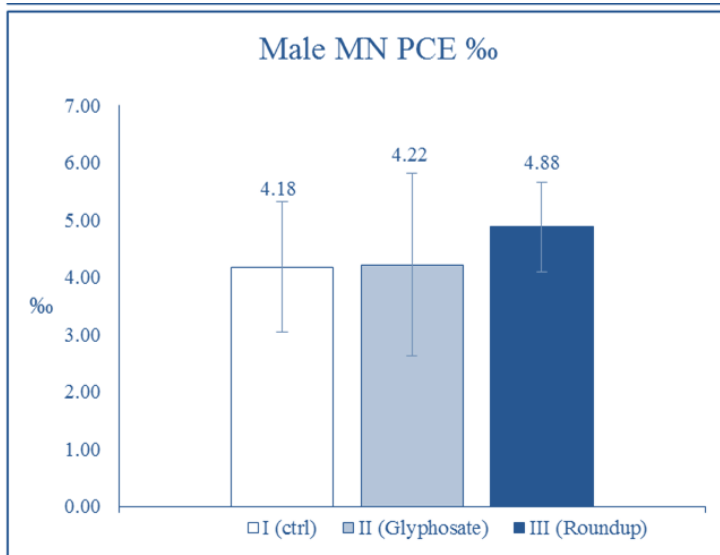


MICRONUCLEI TOXICITY COHORT – results so far...

6 week



13 week





Biological monitoring of workers exposed to carcinogens using the buccal micronucleus approach: A systematic review and meta-analysis

Nancy B Hopf^{1*}, Claudia Bolognesi², Brigitta Danuser¹, Pascal Wild^{1,3}.

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Mutat Res. (2019) 781:11-29. doi: 10.1016/j.mrrev.2019.02.006.



Biological monitoring of workers exposed to carcinogens using the buccal micronucleus approach: A systematic review and meta-analysis

Background

Micronucleus (MN) (extranuclear DNA-containing bodies) frequencies in buccal cells harvested by scraping the inside of the cheeks with a cytobrush

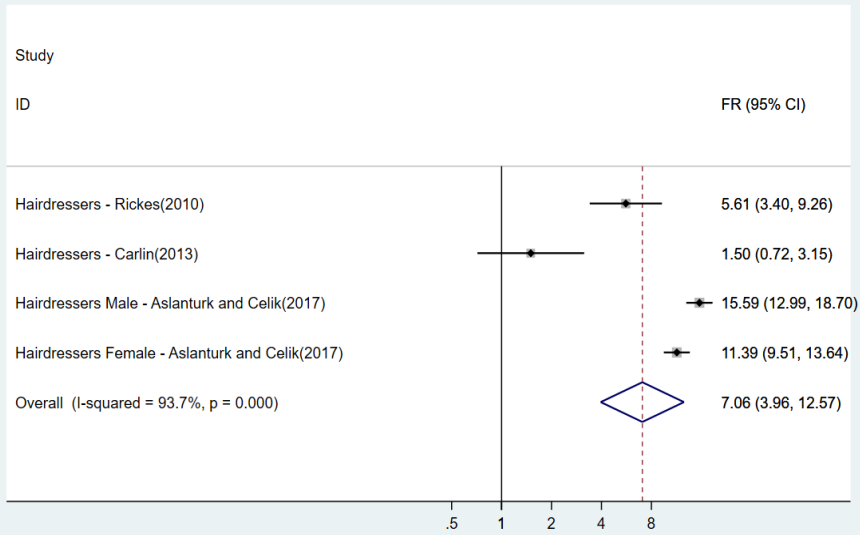
Proposed to monitor workers exposed to aero-digestive carcinogens for early detection of occupational cancer

Assessment of the non-invasive MN approach

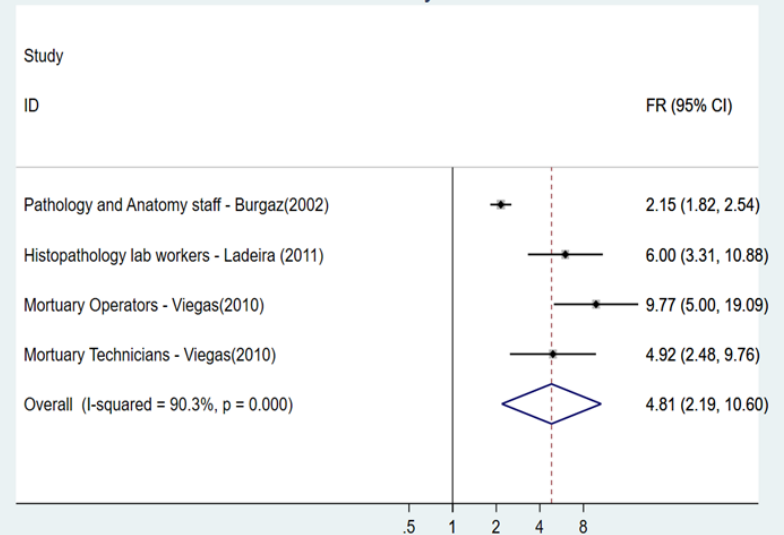
- What is the extent of MN frequency increase in occupationally exposed over non-exposed populations across studies published in the scientific literature for buccal cells; and
- Which types of occupational exposures give relevant summary MN ratios across studies published in the scientific literature.

A systematic literature review was performed, and the MN frequency ratios for buccal cells were calculated for each occupational study.

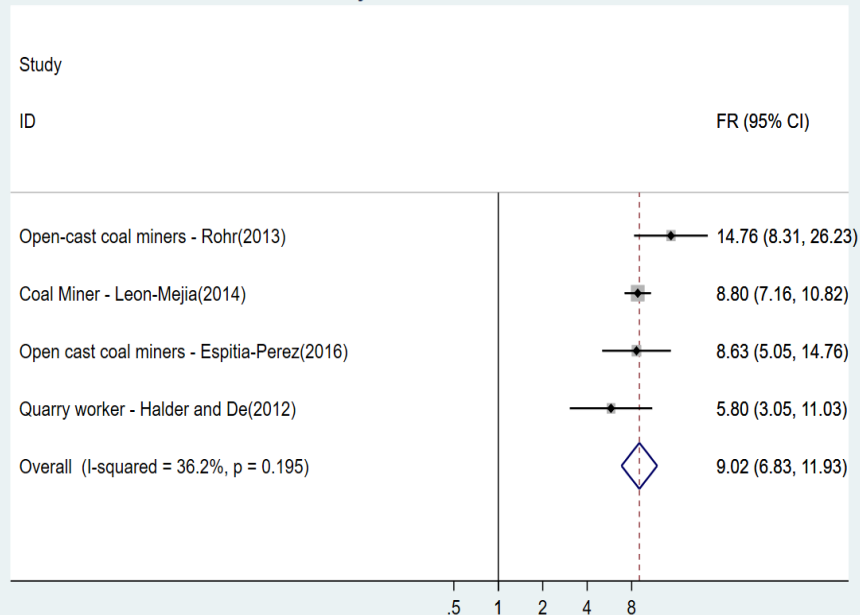
Hairdressers



Formaldehyde



Crystalline silica



silica : FR 9.02 95%CI 6.83-11.93

formaldehyde : FR 4.81 95%CI 2.19-10.60

hairdressers : FR 7.06 95%CI 3.96-12.57



Biological monitoring of workers exposed to carcinogens using the buccal micronucleus approach: A systematic review and meta-analysis

Results

The meta-analysis of the published literature (n=96 studies) showed large random variability between studies within each category ($I^2 > 90\%$),

- except where exposures were to a single carcinogenic substance (e.g. formaldehyde, silica) or
- similar jobs were performed (e.g. antineoplastic dispensing, gasoline attendants).

The unexplained between-study variability can be related to exposures to mixtures of carcinogens with unknown mechanisms.

Conclusion

Better exposure assessments are needed to understand the *relationship between occupational exposures and MN frequency responses in buccal cells*.

Our analysis indicates that the buccal cell MN assay is a promising tool for surveying workers exposed to genotoxic agents



Report from
DiMoPEX Conference Working Group5 Meeting

**“Biomarker of effect and latest developments in
carcinogenicity testing”**

Meeting Organizer: Nancy Hopf,

28-30 October 2019

Venue: Cesare Maltoni Cancer Research Center
Ramazzini Institute, Bentivoglio, Italy
via Saliceto 3, Bentivoglio (BO), 40010

<https://www.ramazzini.org/en/how-to-get-there/>

Local organizer:

Fiorella Belpoggi, Daniele Mandrioli, Fabiana Manservisi



WG 5 meeting outcome

- Submit a Commentary article from the Workshop
- Present the summary of the discussion on Cancer Biomarkers
 - current knowledge on the biology of the biomarker,
 - description of the recommended protocol for the biomarker,
 - possible applications of the assay, and
 - conclusions on knowledge gaps and future developments.
- Structure the commentary as a question and answer for each biomarker to facilitate the reading of these diverse cancer biomarkers.



The following 13 questions were used:

- What is the mechanism (AOPs or MOAs) of this cancer biomarker?
- Is “the biomarker” associated with development of cancer?
- How is “the biomarker” determined?
- How can “the biomarker” be used as surveying exposures to carcinogens?
- How do lifestyle factors affect “the biomarker”?
- Is age related to your biomarker?
- What are possible applications of “the biomarker”?
- How can “the biomarker” be applied as a clinical biomarker?
- How can “the biomarker” be used as a population screening tool?
- What are the limiting factors for applying “the biomarker”?
- What susceptibilities do we need to be aware of when using your biomarker?
- What research is needed to apply “the biomarker” as an individual screening tool?
- What are the ethical issues implement “the biomarker”?

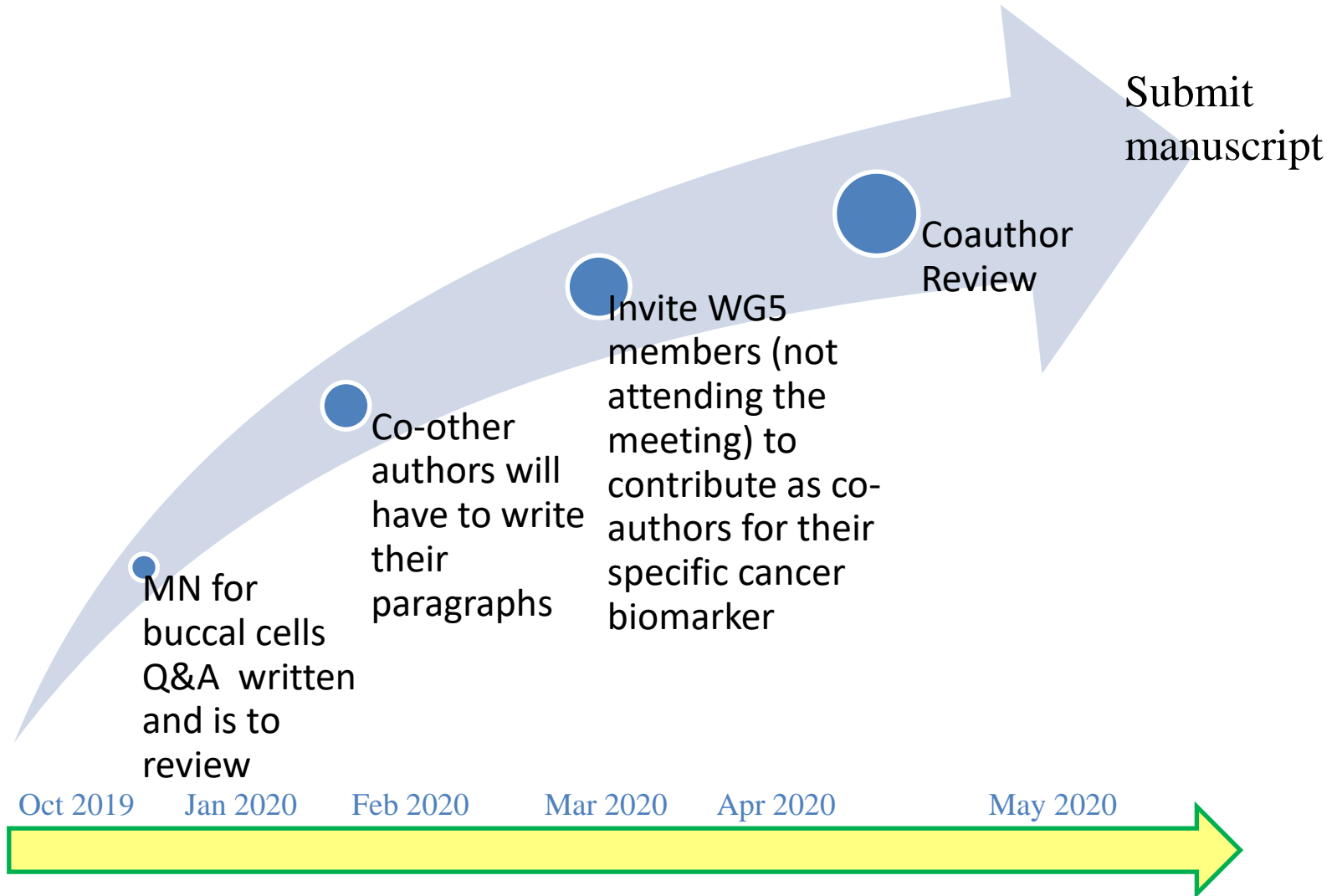


Authors / current assignment

Micronuclei frequency (MN) in blood	[JP Teixeira with P Kossomenos, C Bolognesi, S Bonassi]
Micronuclei frequency in Buccal cells	[NB Hopf with C Bolognesi, A Paschalidou, and Bonassi]
Comet Assay	[M Ghosh with K Nagy, J Puiso]
Aneuploidy (CA)	[author missing]
Histone phosphorylation	[author missing]
Telomere length	[author missing]
DNA adducts	[author missing]
DNA repair capacity	[L Roisman]
Ortho-Tyrosine from EBC	[H Moldovan and R Duca with A Aykut]
Breath analysis for lung cancer	[P Scheepers]
Oxidative stress biomarkers and carcinogens	[H Moldovan and V Valdiglesias]
Epigenetic biomarkers of cancer / GSTP1 methylation	[R Duca]
miRNA exposome	[H Schwartzenbach]
Fungal exposure and cancer	[T Damialis, L Castelyn]
Immunomarkers and cancer	[Stephanie Gilles, Laila Roisman]
Bioassays and cancer	[Fiorella Belpoggio, Fabiana Manservisi]
Occupational physicians role in interpreting biomarkers of exposure and effect	[Doina Giurgiu, Karel Vandamme, Oxzlem Gokzel, Diana Adliene, and Stelian Ioan Morariu]
Calculation of global burden of cancer	[Daria Sgargi, Balasz Adam]



Submission timeline





WG 5 summary

- Training school to standardize laboratory protocols
- Collaboration across countries and institutes possible from the networking meetings
- Review of effect biomarkers for carcinogenic exposures