

**IRSN**

INSTITUT  
DE RADIOPROTECTION  
ET DE SÛRETÉ NUCLÉAIRE

*Faire avancer la sûreté nucléaire*

# Integrating epidemiology and biology for radiation risk assessment.

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MEMBRE DE

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EUROPEAN  
TECHNICAL SAFETY  
ORGANISATIONS  
NETWORK

# Epidemiology and radiation risk assessment.

- Epidemiology has been the main source of scientific evidence on the health effects of ionizing radiation in humans
- Results used to assess risk and define radiation protection standards
- Most informative epidemiological data cover the dose range above 100 mGy of low LET radiation
- At lower dose levels, specific challenges become more pregnant (statistical power, ratio the size of radiation-induced effects compared to the size of effects induced by other factors...)
- However, epidemiology is also proving increasingly informative on **low dose** effects\* and additional results will come in the near future (LSS, Inworks, MWS, Epi-CT...)

\*Shore RE, et al. J Radiol Prot. 2018 Sep;38(3):1217-1233.

# Epidemiology and the very low doses...

- **Below certain dose levels** yet to be determined\*, the challenges faced by classical epidemiology (especially, statistical power) will prevent it from providing directly informative (i.e. sufficiently precise) risk quantification.
  - **Integration of epidemiological and biological knowledge** is expected to further **inform risk extrapolation to very low doses** [Preston et al., 2015].
- > Need for further - indirect - evidence based on links between conjunction of subclinical biological events and health risks

\*depending on the health outcomes considered and possibly population characteristics

# How can epidemiology and radiobiology be integrated?

- Molecular epidemiology [Pernot et al. 2012; Hall et al. 2017; Kreuzer et al. 2015; Seibold et al. 2019].
- Integration of experimental and human data within the Adverse Outcome Pathway (AOP) framework [Preston et al. 2015; Chauhan et al. 2018]
- Modelling : toxicodynamic, mechanistic/biology-based dose-response models [Ruhm et al. 2018; Kaiser et al. 2016], DEBTox, SSD...



# What are AOPs?

**An AOP is a map of the sequence of events that happen after an initial perturbation:**

- Starts with initial interactions of a stressor with a biomolecule in a target cell or tissue (the molecular initiating event or **MIE**)
- Progressing through a dependent series of intermediate “key” events (**KE**)
- Linked together through Key Event Relationships (**KER**) - ideally, quantified
- Culminating with and adverse outcome (**AO**)



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ENVIRONMENT DIRECTORATE  
JOINT MEETING OF THE CHEMICALS COMMITTEE AND THE WORKING PARTY  
ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

Cancels & replaces the same document of 27 January 2017

## Graphical Representation of the AOP

A graphical summary of the AOP listing all the KEs in sequence, including the MIE (if known) and AO, and the pair-wise relationships (links or KERs) between those KEs should be provided. This is easily achieved using the standard box and arrow AOP diagram (Figure 1).

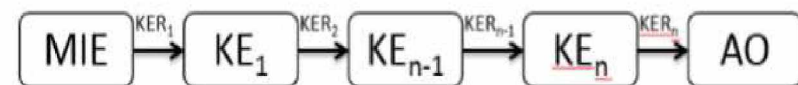
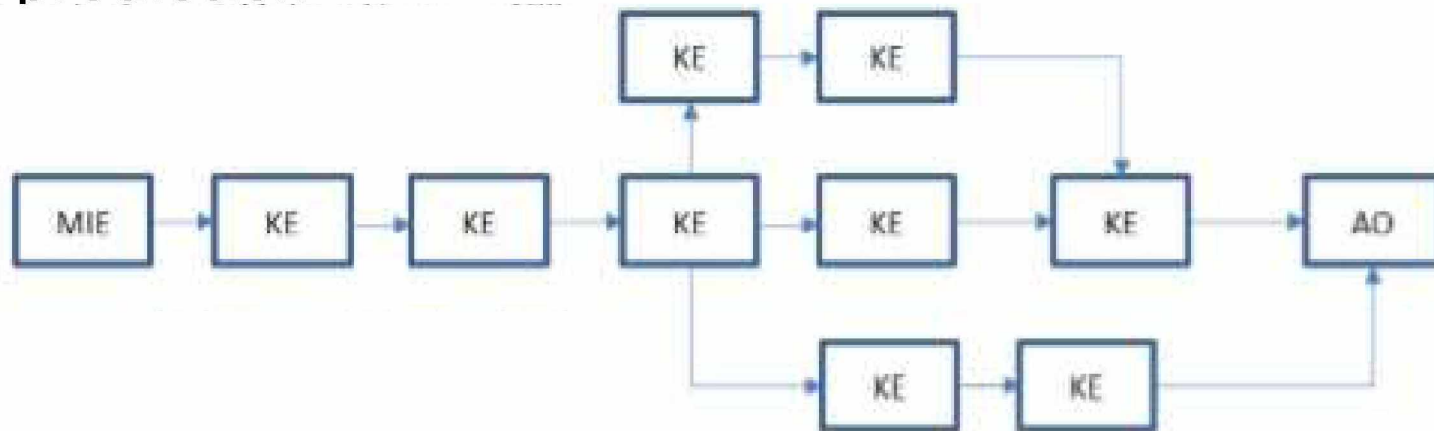


Figure 1. Example of a generic AOP diagram in its simplest form (see also [https://aopwiki.org/aops/23#graphical\\_representation](https://aopwiki.org/aops/23#graphical_representation))

# A few key principles of AOPs:

1. AOPs are not stressor - specific
2. AOPs are modular
  - Key events and relationships can be shared by multiple AOPs
3. As a construct, an individual AOP is composed of a single sequence of KEs and KERs leading to a single AO
4. But AOP networks will emerge and be the basis for prediction



5. AOPs are living documents

# Practical view on AOP

## A framework for organizing data

- Integrate all types of information at different levels of biological complexity
- Ultimate goal : to link these events well enough that the upstream molecular data can be used to predict the downstream outcomes.

-> The AOP framework is the basis of **predictive toxicology**...

**Promoted by the US EPA and OECD for chemical risk assessment**



# Proposed application to ionizing radiation

## INTEGRATING BASIC RADIOBIOLOGICAL SCIENCE AND EPIDEMIOLOGICAL STUDIES: WHY AND HOW

R. Julian Preston\*

“It is proposed that the key-event approach be used in conjunction with enhanced radiation epidemiology data to reduce overall uncertainty in low dose/low dose-rate cancer and non-cancer risk estimates.”

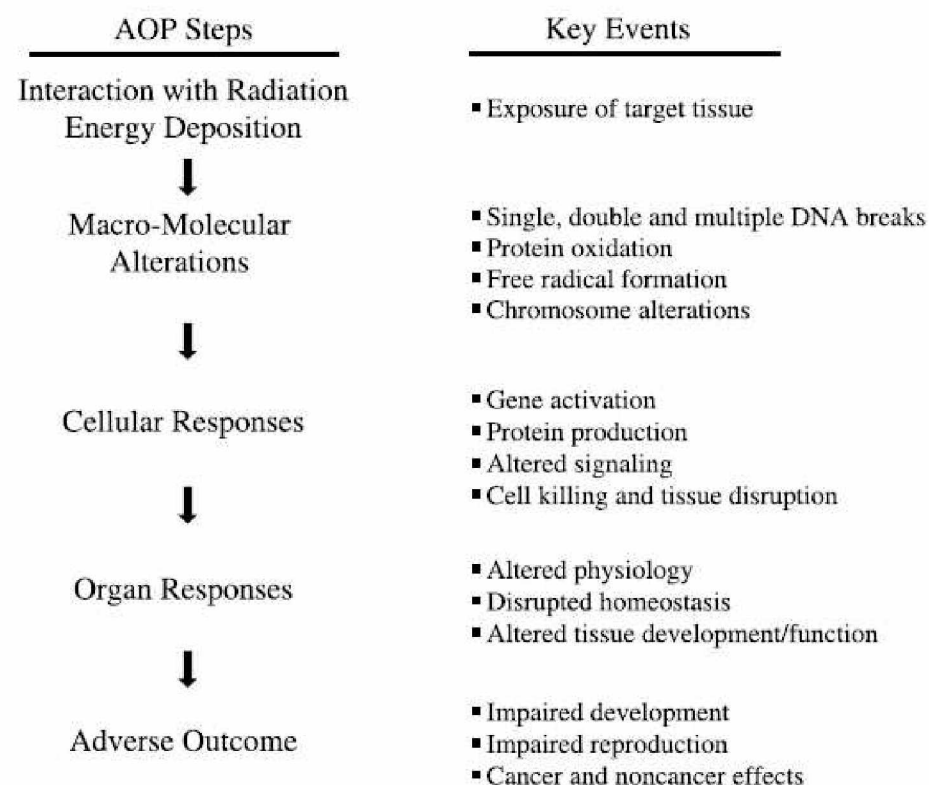
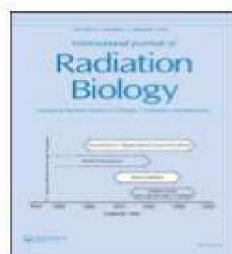


Fig. 1. Schematic representation of an AOP for ionizing radiation-induced cancer and non-cancer diseases showing each step along the proposed pathway and the associated key events.

\* [Health Phys.](#) 2015 Feb;108(2):125-30



# Early application to ionizing radiation



International Journal of Radiation Biology

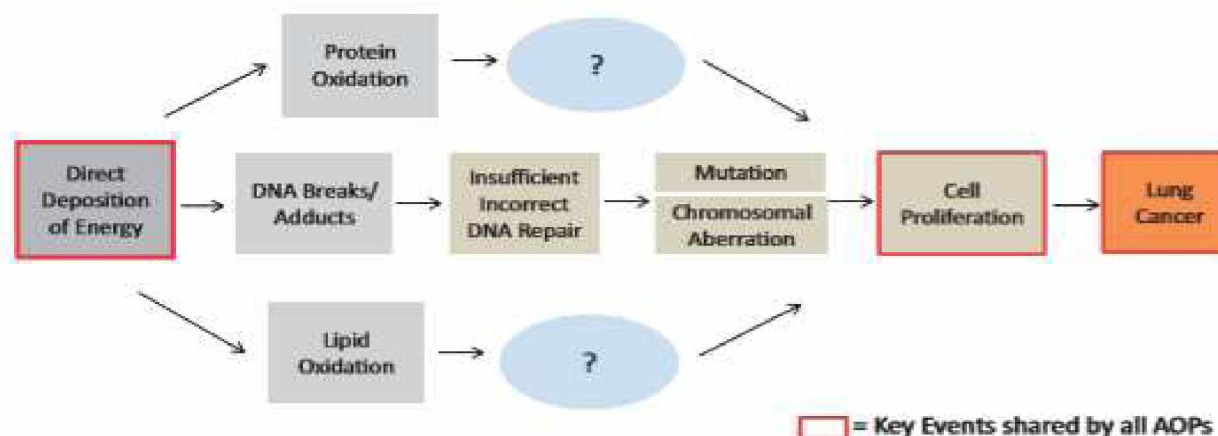


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## Is there a role for the adverse outcome pathway framework to support radiation protection?

Vinita Chauhan, Zakaria Said, Joseph Daka, Baki Sadi, Deepti Bijlani, Francesco Marchetti, Danielle Beaton, Adelene Gaw, Chunsheng Li, Julie Burtt, Julie Leblanc, Marc Desrosiers, Marilynne Stuart, Mathieu Brossard, Ngoc Q. Vuong, Ruth Wilkins, Sami Qutob, James McNamee, Yi Wang &

6 V. CHAUHAN ET AL.



**Figure 4.** A hypothetical example of how an AOP can help define knowledge gaps by bringing data together in a form of a network of key events starting from the molecular initiating event, i.e. deposition of energy (direct) to multiple key events that converge to cause an adverse outcome (AO), i.e. lung cancer.

# Prediction requires... quantitative data to build quantitative AOPs (qAOPS)

For instance, relationships between key events (KERs) can be partly quantified by **molecular epidemiology** (depending on sample acceptability, accessibility, etc...)

[Pernot et al; 2012; Hall et al 2017; Kreuzer et al 2015; Seibold et al 2019]

**Ideally** : use cohorts documenting all events from radiation exposure (MIE) until radiation induced diseases (AO), including all intermediate key events (KE)

**Alternatively, combine information from:**

- **radiation exposed** molecular epidemiology **cohorts** (from MIE to key events)
- **from non specific** molecular epidemiology **cohorts** that can document relationships between late / non specific key events and adverse outcomes

-> **"meet in the middle"** approach [Vineis P & Perera 2007]

...expect multiple predictors (qAOP networks for prediction)



# Biologically-based dose response models

Consider **quantitative relationships between KEs based on current understanding** of biological processes

In the **radiation field, mostly applied** to KEs of the carcinogenesis process as two-stage clonal expansion (**TSCE**) or similar models [Ruhm et al 2017]

-> **Flexible**, more stages and future knowledge on biological processes can be added

Already applied to several cohorts without biosamples [Ruhm et al 2017]

But also with a biomarker (overexpression of the CLIP2 gene) for the study of post-Chernobyl thyroid cancers [Kaiser et al 2016]

Recent application to circulatory diseases development in Mayak [Simonetto et al 2017]

# What kind of evidence can and should be considered while building AOPs for radiation

## 1. Experimental data ....

- In vitro
- In vivo

## 2. Simulation (in silico) data

## 3. “Classical” epidemiological data

- Using “empirical” models
- Using biological-based models

## 3. Molecular epidemiology data

- From radiation exposed cohorts
- But also from non radiation-exposed cohorts

## Toward identification/ validation of key events

### Graphical Representation of the AOP

A graphical summary of the AOP listing all the KEs in sequence, including the MIE (if known) and AO, and the pair-wise relationships (links or KERs) between those KEs should be provided. This is easily achieved using the standard box and arrow AOP diagram (Figure 1).

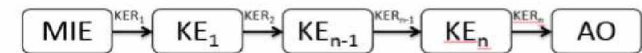
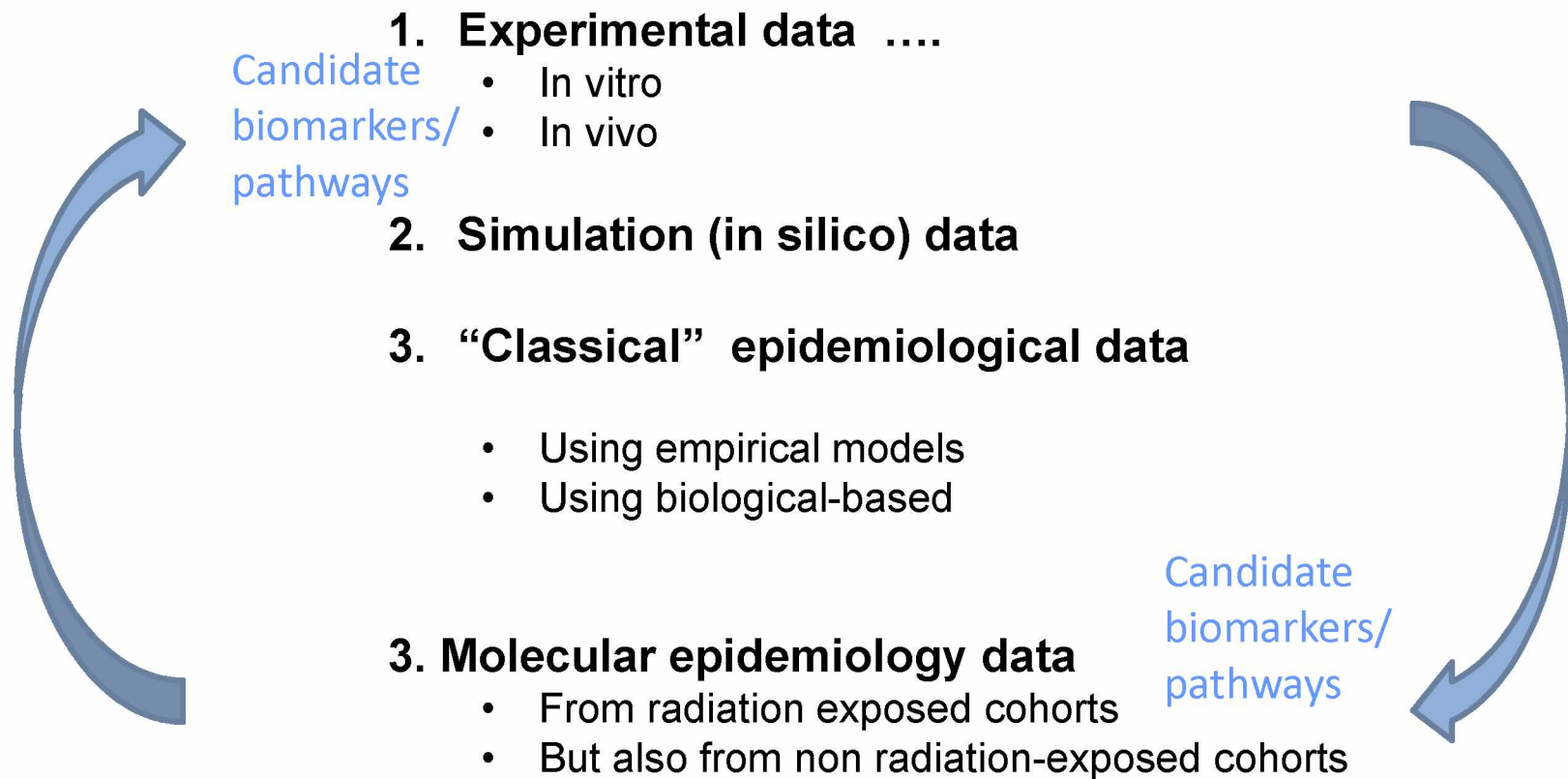


Figure 1. Example of a generic AOP diagram in its simplest form (see also [https://aopwiki.org/aops/23#graphical\\_representation](https://aopwiki.org/aops/23#graphical_representation))

## Toward QUANTIFICATION of key event relationships

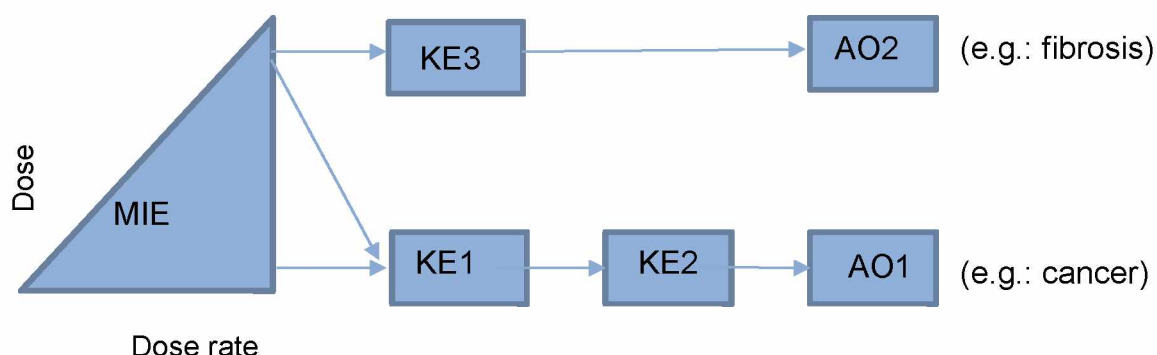
# What kind of evidence can and should be considered while building AOPs for radiation



Possible discovery and validation loop for biomarkers

# Challenges related to the development of (quantitative) AOPs for ionizing radiation

- integration of data from **various models** (human, animal, cell...)
- integration of **temporal sequence** of events
- **Scarcity of biological** samples for molecular epidemiology
- Different **key events** may occur depending on dose and/or dose rates, e.g.:



But also according to **particle type / radionuclide** (internal contamination)...

-> **Adapt the general framework** or rather treat separately typical **scenarii of exposure** (e.g.: radon, radioiodine exposure, etc)?

# Some advantages of the AOP framework

- **Flexible framework** to integrate information from different levels/disciplines
- Improved **organisation of current knowledge**
- Improved **communication**
- Easier **identification** of critical **data gaps** (to be filled by new studies)
- Favors **linkage with data produced in other fields** (e.g.: chemical toxicology) – KERs will increasingly be quantified
- KE specific to certain species, or common to several ones, can be properly identified -> potential for **better integrated** radiation protection of **humans** and the **environment**.



# Conclusions

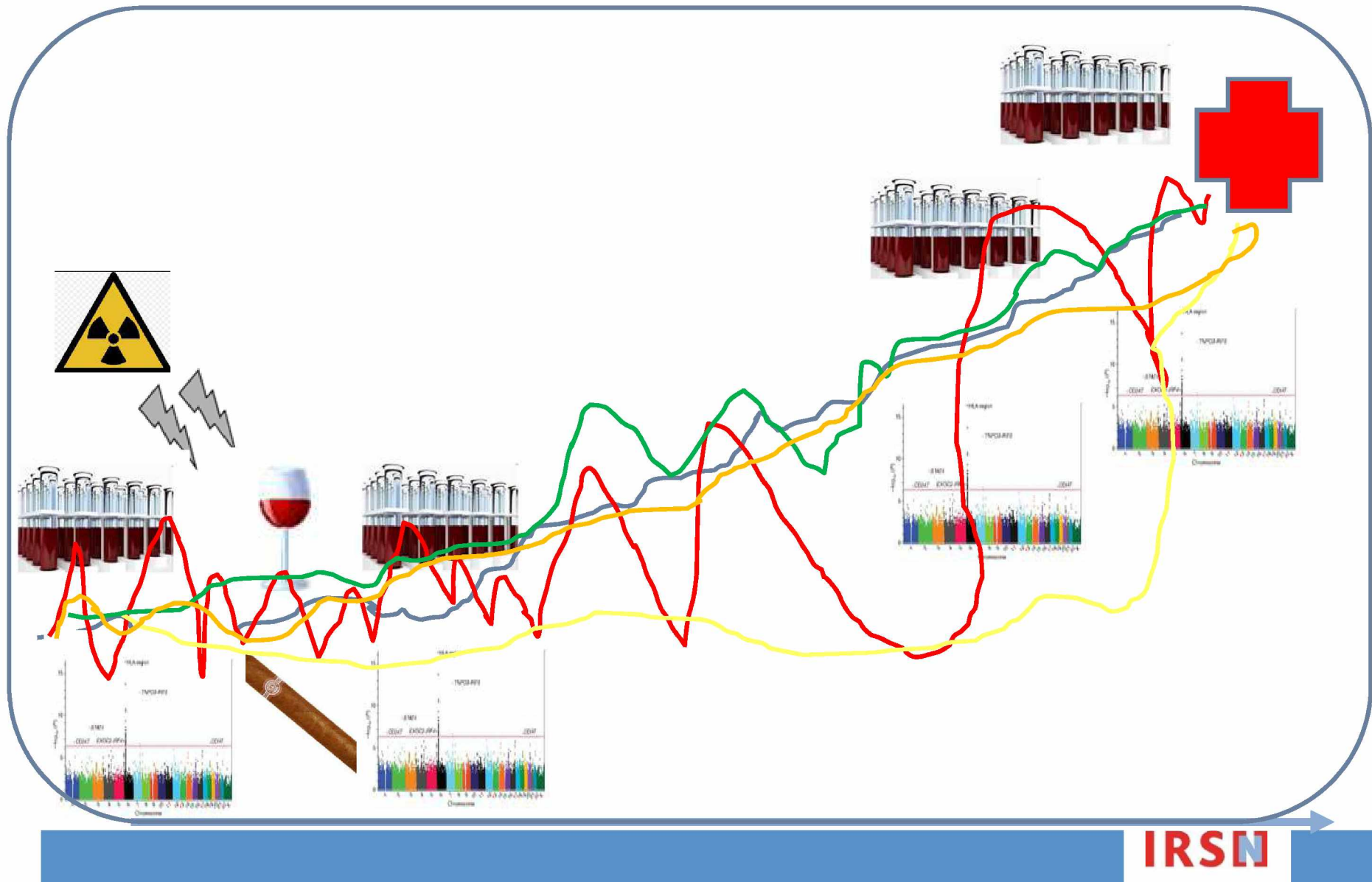
- **Classical epidemiology** will be **increasingly informative** on the effects of **low doses** over the forthcoming years (e.g.: EpiCT, Million Workers Study, INWORKS...)
- **Integration** of epidemiology and radiobiology will be key to get insight (mostly indirect) into the health effects of **very low doses**
- **Molecular epidemiology** can be helpful that purpose, in conjunction with other radiobiology data (e.g.: experimental and *in silico*)
- BBDR and other types of **models** will be needed
- Need for **multidisciplinary** efforts, including contribution from the more AOP-experienced non-radiation (e.g. chemical toxicology) community





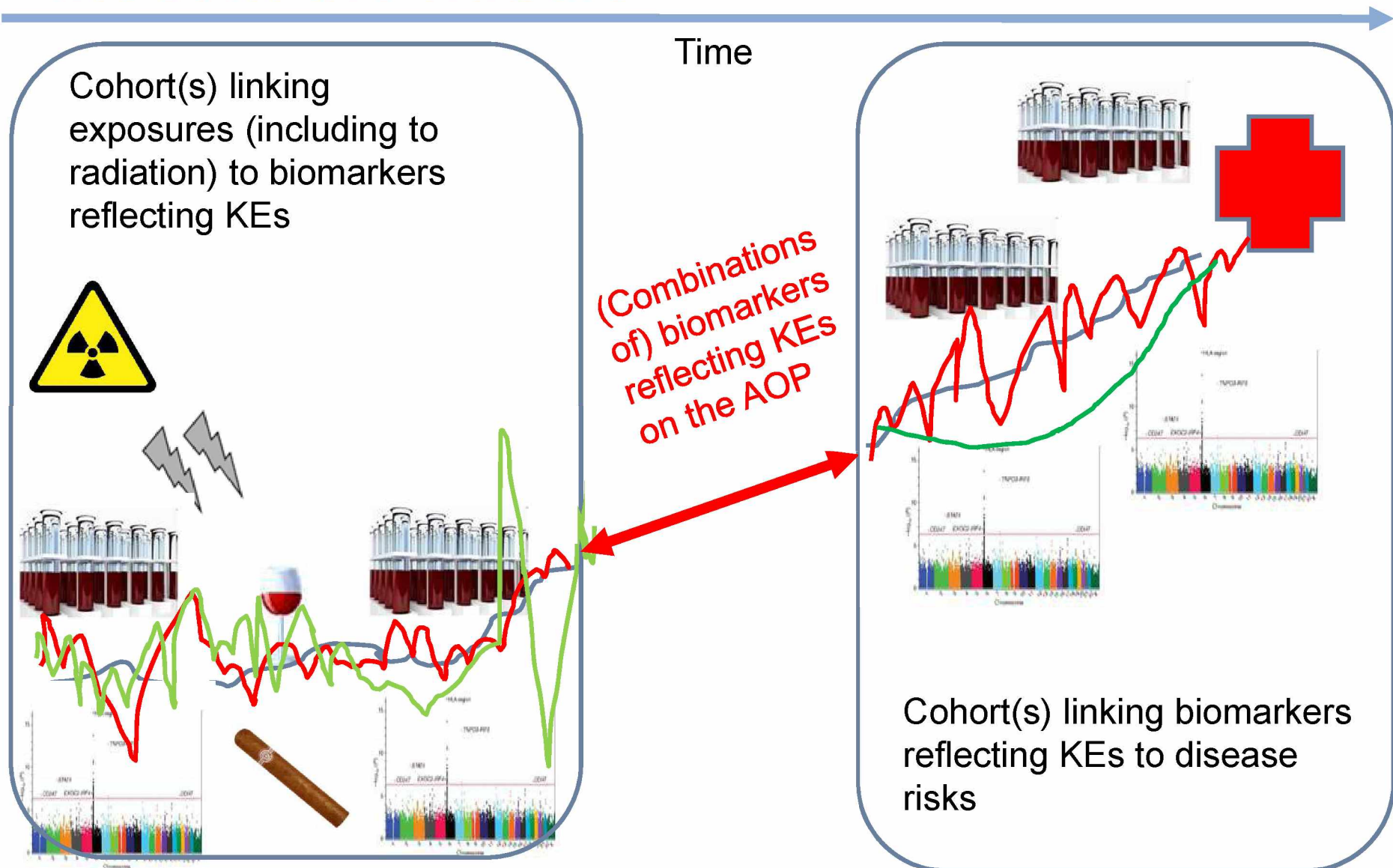
Thank you for your attention

# *“Ideal” cohort and follow-up scheme...*



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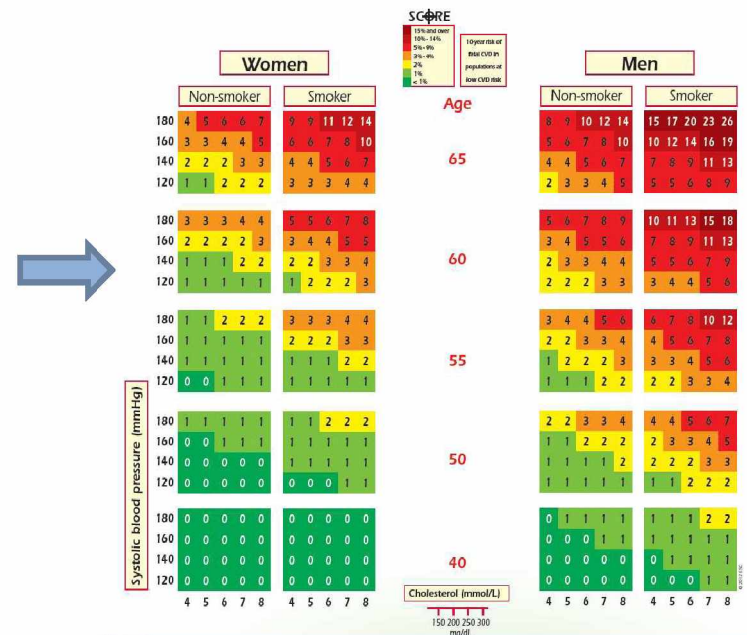
# *“Meet in the middle”*



# Developing risk prediction based on multiple biomarkers using large population-based cohort studies with biobanks?

E.g. following the model of the SCORE (Systematic coronary risk evaluation) for circulatory diseases

- 12 European cohorts
- 250,000 people
- 3 million person-years
- 7,000 cardiovascular events



10-year circulatory risk according to age, sex, cholesterol and smoking

“Classical” risk factors used in the SCORE (age, sex, cholesterol, smoking...) might be replaced with new biomarkers (discovered using OMICs, other techniques?)



## “Meet in the middle”

Identifying the overlap between markers of exposure and predictive markers of disease outcome has previously been defined as a “meet-in-the-middle” approach (Vineis and Perera, 2007). According to that original concept, the finding that preclinical biomarkers shown to be related to particular exposures in prospective studies are also elevated in certain subclasses of disease would strengthen causal links between exposures and disease.

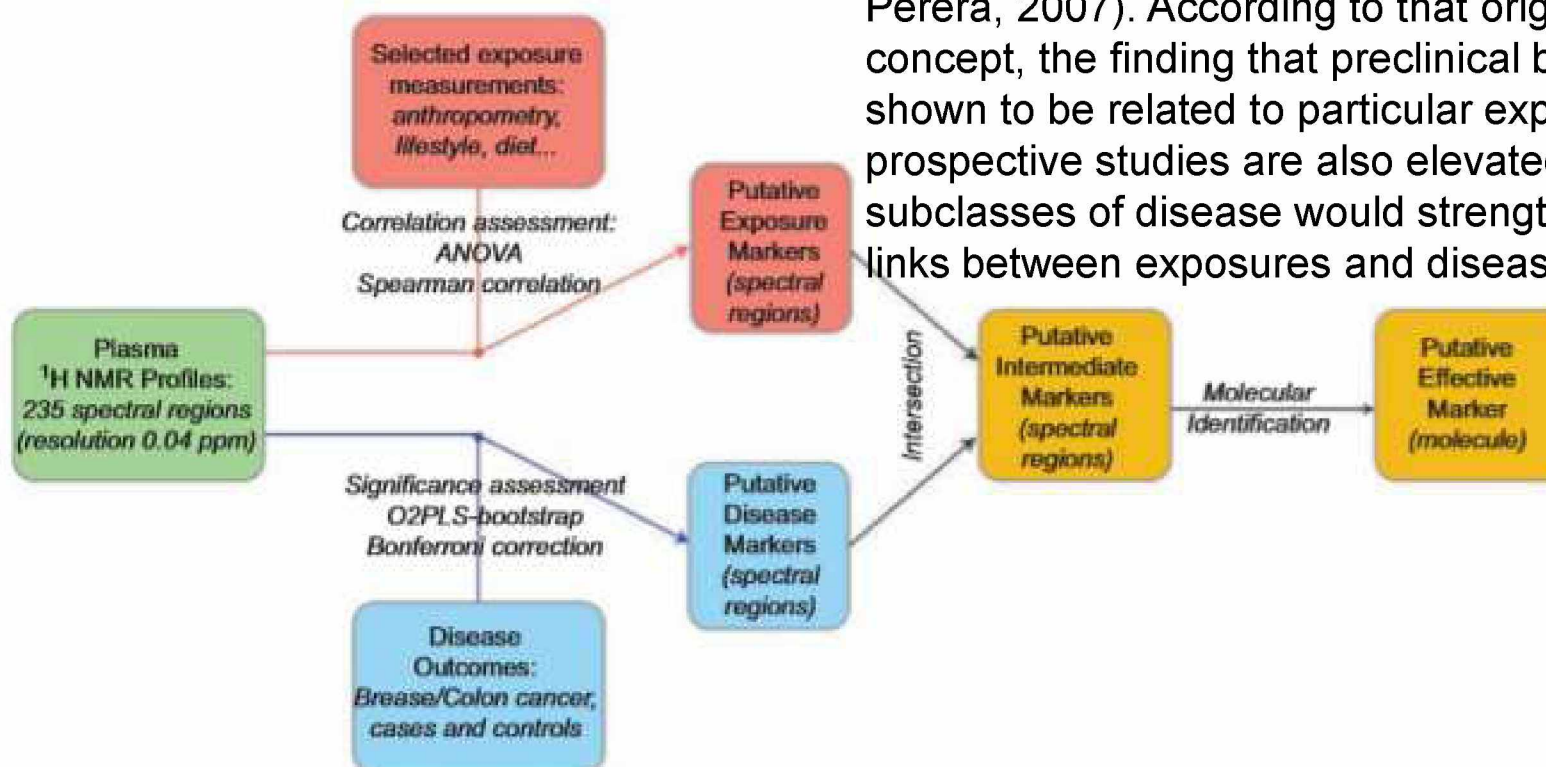
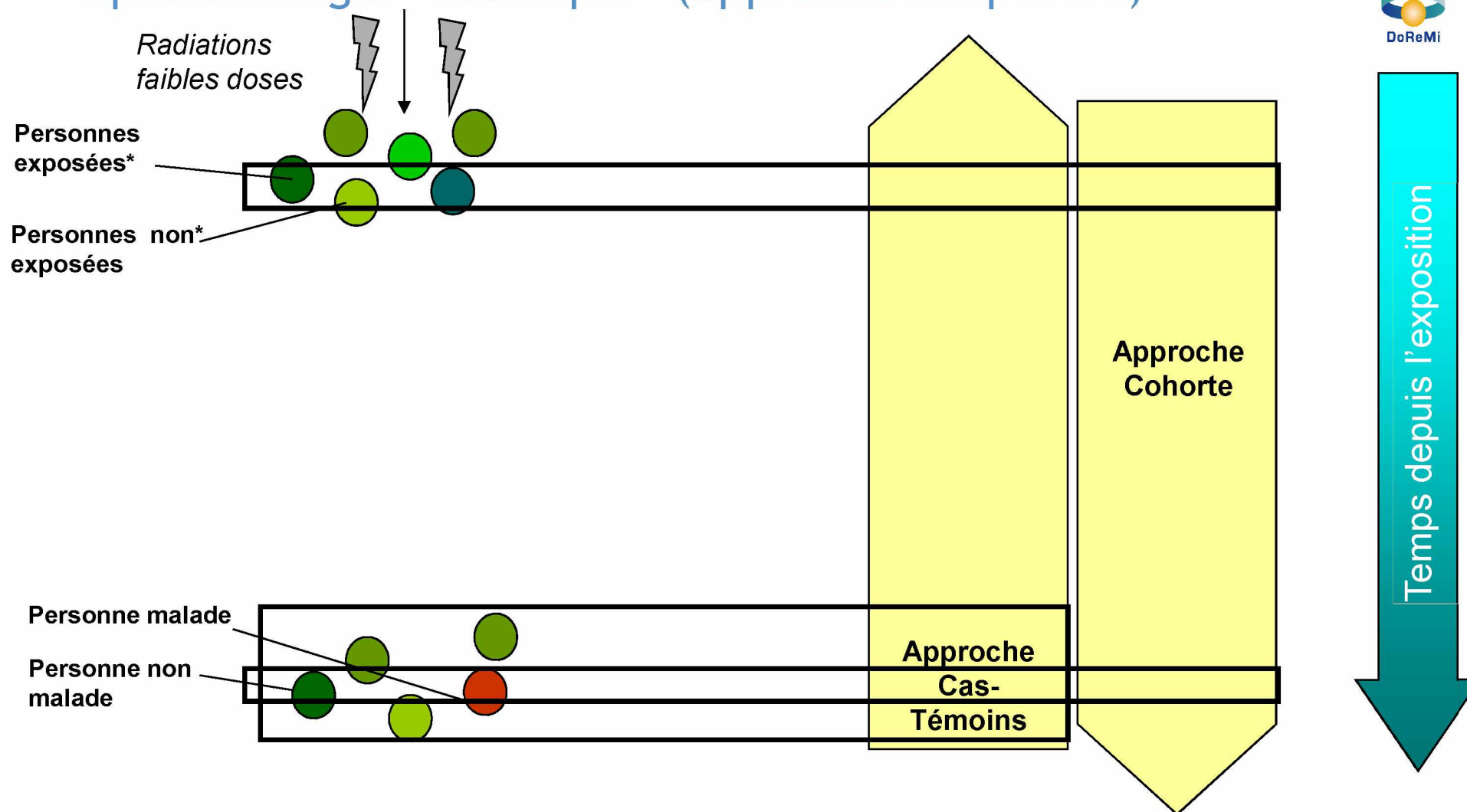


Figure 1. Schematic representation of the implementation of the ‘meet-in-the middle’ approach.

[Chadeau-Hyam et al, Biomarkers, 2011; 16(1): 83–8]

# Epidémiologie “classique” (approche simplifiée)

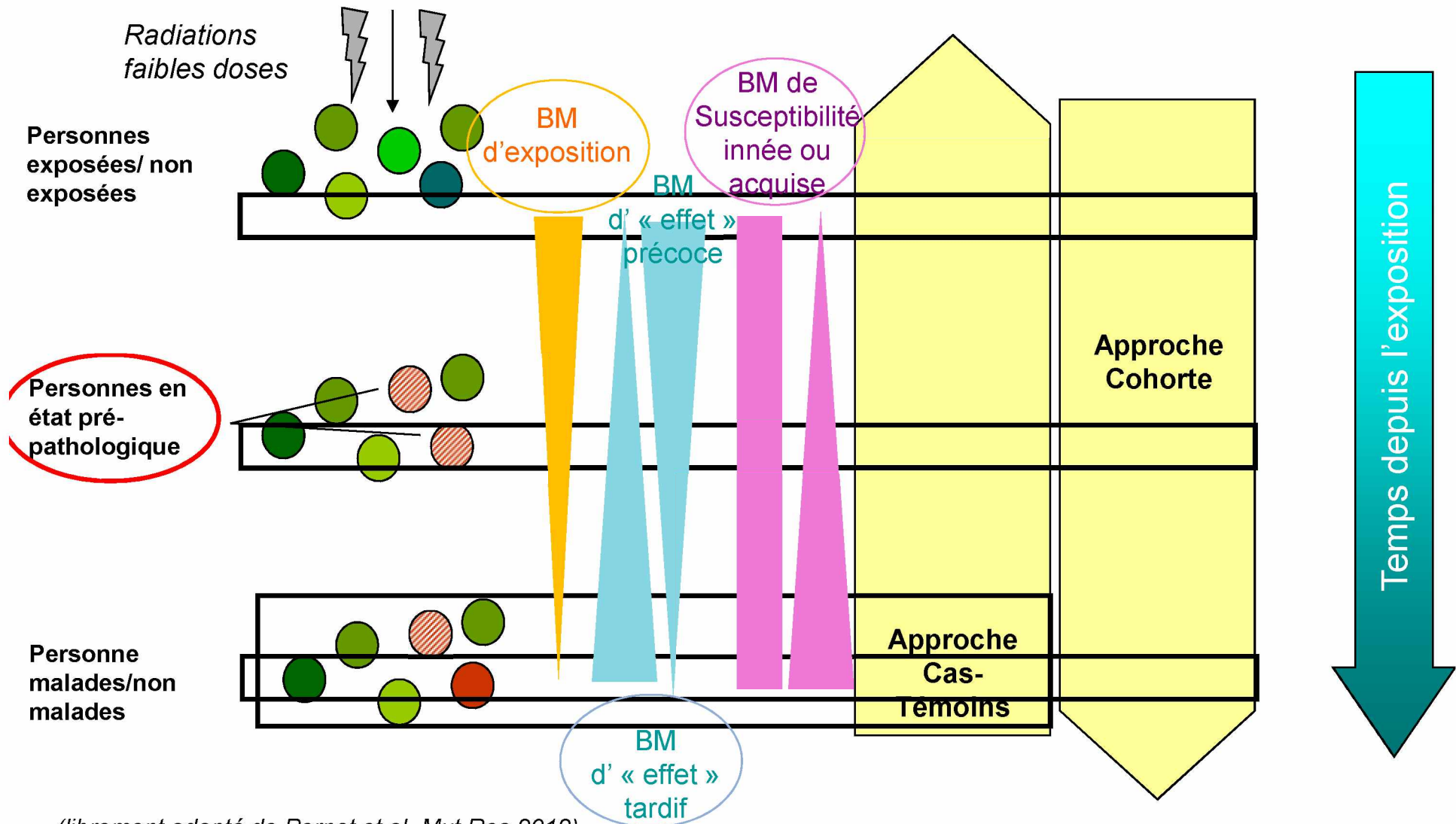


(librement adapté de Pernot et al, Mut Res 2012)

\*ou plus ou moins exposées



# Epidémiologie moléculaire, intégrant des biomarqueurs (BM)



(librement adapté de Pernot et al, Mut Res 2012)

## *Exemples études d'épidémiologie moléculaire de grande ampleur en population générale : UK Biobank*

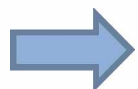
- Cohorte **prospective de 500 000** adultes (40 à 69 ans à l'inclusion (2007-2010))
- **Consentement large** pour suivi et tout type d'analyse sur la santé
- Données sur le mode de vie, l'environnement, l'histoire médicale personnelle et familiale
- Mesures physiques et cliniques (pression artérielle, BMI, spirométrie, vision...)
- **Prélèvements biologiques** (sang, plasma, sérum, cellules, urine, salive),
- **Biobanque automatisée -80°C**



## *Exemples études d'épidémiologie moléculaire de grande ampleur en cours : UK Biobank*



- **Suivi individuel, croisement** avec les bases de données de santé nationales (incidence, mortalité, données hospitalières)
- **Etudes complémentaires sur sous échantillons**  
(alimentation, expositions professionnelles, fonctions cognitives, fréquence cardiaque en continu, IRM cerveau...)
- **Possibilité de croisement** avec autres bases de données épidémiologiques



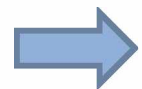
**Objectifs larges** : améliorer la prévention, le diagnostic et le traitement des maladies chroniques

**Données accessibles** au monde de la recherche (académique et privée)

## *Exemples études d'épidémiologie moléculaire de grande ampleur en cours (megacohortes)*

Etudes **similaires** à UK biobank :

- Constances (France, 200,000 adultes)
- German National Cohort - NAKO (Allemagne, 200,000 adultes)
- EPIC (Europe, 520,000 adultes) ...



**Retombées attendues** multiples:

**Niveaux** de référence de **BM**s en population générale,

Variabilité intra/inter individuelle, identification des **facteurs influents**

Identification de **nouveaux BM**...

Quantification des **associations BM/pathologies**, utiles à la prédiction des **risques**