Funded by the European Union

INTEGRANO

MULTIDIMENSIONAL INTEGRATED QUANTITATIVE APPROACH TO ASSESS SAFETY AND SUSTAINABILITY OF NANOMATERIALS IN REAL CASE LIFE CYCLE SCENARIOS USING NANOSPECIFIC IMPACT CATEGORIES

Formalizing the Exposure Assessment Process

TSCA Occupational Exposure Workshop: Data & Modeling

15 May 2024

Joonas Koivisto[1,2], Michael Jayjock[3], and Susan Arnold[4]

[1]ARCHE Consulting, Wondelgem, Belgium
[2]University of Helsinki, Helsinki, Finland
[3]Jayjock Associates, LLC,Langhorne, PA, USA
[4]School of Public Health, University of Minnesota, MN, USA

This project has received funding from the European Union's Horizon Europe research and innovation programme under GA No 101138414

Our Bias and Assertions Regarding Exposure Modeling

1. Properly supported, first principle models will provide the tools necessary to do a cost-effective and accurate determination of exposure potential.
2. Evaluation studies of commonly used first principle models such as those included in IH-MOD have shown them to be appropriately health-conservative
3. First principle models need to be supported with investment to develop resources to establish a database of relevant sources.
4. Such development will be universally useful and, as such, could be developed as a worldwide public works project.

Funded by
the European Union

Content: EPA's Opportunity to Establish a Strong Basis for Exposure Assessment

- Exposure assessment and applications
  - Personal exposure measurements
  - Exposure modellings
- Regulatory criteria for exposure models
  - Contextual criteria
  - Numerical criteria for models' performance
- Regulatory compliance of
  - mass-balance models
  - ECHA R.14 recommended models
- Relevant exposure determinants
- Some development requirements
- Summary

Workplace measurements

Requirements in workplace exposure measurements (EN 689)

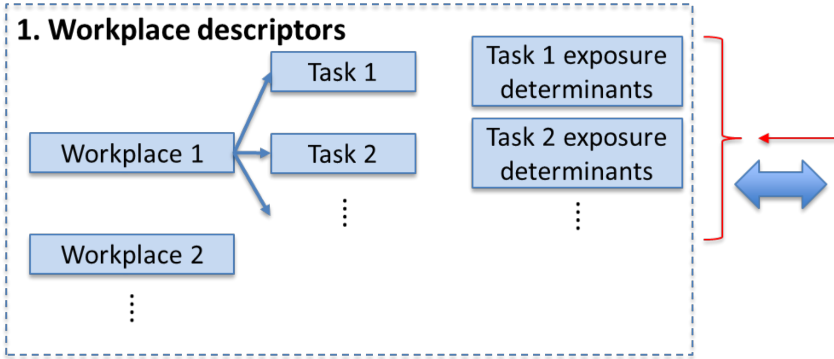
- **Operational conditions in each task:**
  - Process and process parameters
  - Emission controls
  - Background sources
  - Room ventilation and volume
  - Other potential exposure determinants
- **Worker behavior:**
  - Job classification
  - Tasks, task durations, and frequencies
  - Experience of the worker (personal working practices)

Applications of the workplace measurements:

- Regulatory exposure compliance (EN689)
- Constitution of similar exposure groups (SEGs). Applications:
  - Reduce frequency of personal measurements
  - Predict exposures in another factory with similar OCs and worker behavior or conditions that favors lower exposure
- Exposure model testing (requires process emission rates/factors)

- **NOTE, extrapolation for other than SEGs is not possible**

Recap: Efficient data collection is based on existing workplace descriptors to which worker activity is linked.



2. Exposure

Measurement	Exposure, [mg/m³]
Workplace 1: • T1 140 min • T2 100 min • T3 60 min	0.01
	0.02
	0.03
Workplace 1: • T1 150 min • T2 150 min	0.001
	0.002
	0.003
⋮	⋮

Requirements:

- Registration of workplace exposure determinants
- Measurer register performed tasks during sample collection

INTEGRANO

Exposure modellings

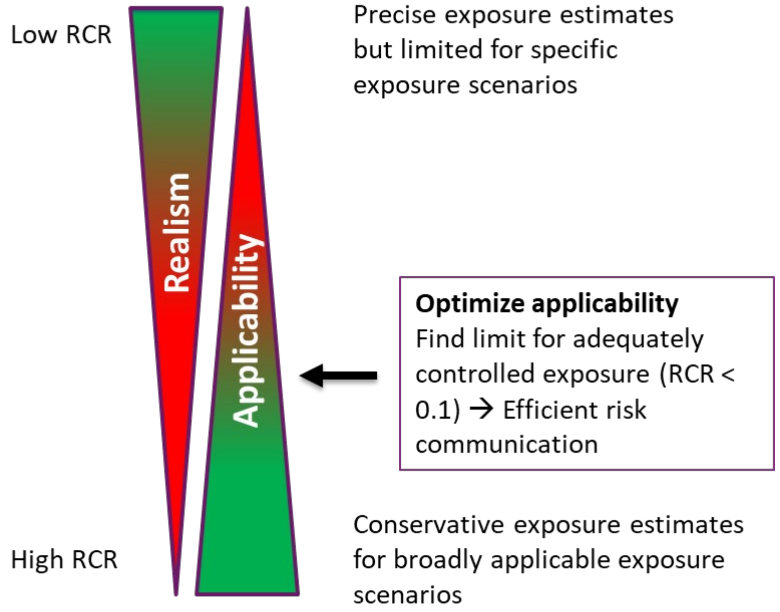
Requirements in exposure modelling:

- **Operational conditions in each task:**
  - Process and process parameters
  - Process emission rates/factors
  - Emission controls
  - Background sources
  - Room ventilation and volume
  - Other potential exposure determinants
- **Worker behavior:**
  - Tasks, task durations, and frequencies

Applications:

- Regulatory exposure compliance in different OCs (EN689)
- Setting safe conditions of use (CoU)
- Optimizing exposure controls (designing efficient mitigation)
- Derive priorities for measurements

Recap: Setting safe conditions of use (Koivisto et al. 2021; 2022, Koivisto and Arnold, 2023)



When is exposure adequately controlled?

- **The predicted exposure risk is considered highly-controlled when a 95th percentile (P95) of the exposure distribution is below 10% of the occupational exposure limit value (Torres et al 2014; Hewett et al. 2006)**

How about allocation factors?

- **Limits for integrated exposure (occupational and public exposure)?**
- **Process specific limit, i.e. how much one process machine can increase the exposure (e.g. P95 < 0.01 × OEL)?**

Funded by
the European Union

INTEGRANO

Exposure model regulatory compliance

- ECHA does not have quality criteria for exposure models
- Criteria in US-EPA (2019) Guidelines for Human Exposure Assessment is based on NRC (2007)

Box 5-5. Guidance Documents and Resources to Support Modeling Efforts

- WHO (2005) *Principles of Characterizing and Applying Human Exposure Models.*
- NRC (2007) *Models in Environmental Regulatory Decision Making.*
- U.S. EPA (2009d) *Guidance on the Development, Evaluation, and Application of Environmental Models.* EPA/100/K-09/003.
- *Center for Exposure Assessment Modeling (CEAM) website. U.S. EPA.*
- *Radiation Protection Document Library* website. *Radiation Protection* website. U.S. EPA.
- *Predictive Models and Tools for Assessing Chemicals under the Toxic Substances Control Act (TSCA)* website. U.S. EPA.

US-EPA (2019)

- NRC provides only recommendations but does not define a numerical standard for accuracy that all models must attain before they can be used in the decision-making process (Box 4-2)
- Similar criteria given by
  - Daubert (Jayjock et al. 2011)
  - Nicas et al. (2021)
- EPA has the responsibility to ensure that a model's development and use is transparent (NRC, 2007).
- Models developed outside of the agency must meet the same acceptability and application criteria as models developed within EPA (NRC, 2007)

BOX 4-2 Individual Elements of Model Evaluation

NRC (2007)

Scientific basis – The scientific theories that form the basis for models.

Computational infrastructure – The mathematical algorithms and approaches used in the execution of the model computations.

Assumptions and limitations – The detailing of important assumptions used in the development or application of a computational model as well as the resulting limitations in the model that will affect the model's applicability.

Peer review – The documented critical review of a model or its application conducted by qualified individuals who are independent of those who performed the work, but who are collectively at least equivalent in technical expertise (i.e., peers) to those who performed the original work. Peer review attempts to ensure that the model is technically adequate, competently performed, properly documented, and satisfies established quality requirements through the review of assumptions, calculations, extrapolations, alternate interpretations, methodology, acceptance criteria, and/or conclusions pertaining from a model or its application (modified from EPA 2006a).

Quality assurance and quality control (QA/QC) – A system of management activities involving planning, implementation, documentation, assessment reporting, and improvement to ensure that a model and its component parts are of the type needed and expected for its task and that they meet all required performance standards.

Data availability and quality – The availability and quality of monitoring and laboratory data that can be used for both developing model input parameters and assessing model results.

Test cases – Basic model runs where an analytical solution is available or an empirical solution is known with a high degree of confidence to ensure that algorithms and computational processes are implemented correctly.

Corroboration of model results with observations – Comparison of model results with data collected in the field or laboratory to assess the accuracy and improve the performance of the model.

Benchmarking against other models – Comparison of model results with other similar models.

Sensitivity and uncertainty analysis – Investigation of what parameters or processes are driving model results as well as the effects of lack of knowledge and other potential sources of error in the model.

Model resolution capabilities – The level of disaggregation of processes and results in the model compared to the resolution needs from the problem statement or model application. The resolution includes the level of spatial, temporal, demographic or other types of disaggregation.

Transparency – The need for individuals and groups outside modeling activities to comprehend either the processes followed in evaluation or the essential workings of the model and its outputs.

Funded by
the European Union

Numerical criteria for exposure model regulatory compliance

ASTM D5157-97 Standard Guide for Statistical Evaluation of Indoor Air Quality Models

ASTM D5157-97: Model performance is considered adequate when the five criteria are simultaneously met.				
Correlation coefficient r ≥ 0.9	Slope of the regression line b = 0.75 - 1.25	Intercept of the regression line a ≤ (0.25 x average predicted concentrations)	Normalized Mean Square Error (NMSE) ≤ 0.25	Normalized bias (Fractional Bias or FB) ≤ 0.25

Compliance with the Dutch Social Economic Council (Rijksoverheid) (ref N/A)

Compliance with the Dutch Social Economic Council (Rijksoverheid)							
Comparisons (criteria: n≥20 and Spearman correlation ≥0.6)						The tool estimates a reasonable worst-case which represents the upper-end side of possible exposure values.	Measurements do not exceed the model estimates for more than 10% of the total comparisons.
Solids		Liquids		Gases/fumes			
n	Spearman corrleation	n	Spearman corrleation	n	Spearman corrleation		

Examples of events that make models no longer acceptable (NRC 2007) :

1) The model has been shown to produce erroneous results (false positives or false negatives;
2) Alternative approaches with higher reliability are available and can be developed without unreasonable costs; and
3) Key inputs required by the model are found to be incorrect or out of date

Numerical compliance justifies the model applicability, but for reasonable decision making, optimal accuracy and precision should be considered → Tiered approach

Regulatory compliance of NF/FF model

Criteria	Result
Scientific pedigree	**Complied:** e.g. Hemeon (1963); Nazaroff and Cass (1989); Nicas (1996); Jayjock et al. (2011), Seinfeld and Pandis (2016)
ASTM D5157-97	**Complied for VOCs**: Arnold et al. (2017), NF 96% compliance with toluene, 88% compliance with 2-butanone, 11% compliance with acetone (3x3 tests in total)
Daubert criteria	**Complied:** Jayjock et al. (2011)
The Dutch Social Economic Council (Rijksoverheid)	**Complied for VOCs**: Abattan et al. (2021), Jayjock et al. (2011) **Partial compliance for particulate matter:** Koivisto et al. (2019), In 38 scenarios ratio of predicted and measured GM varied from 0.82 to 1.46. N/A for liquids: Unclear if liquids are part of volatiles
Nicas et al. (2021)	E.g. IH-MOD 2.0 (NF/FF model)

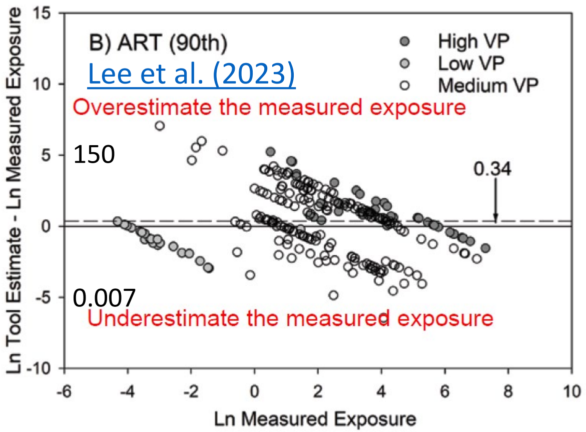
Funded by
the European Union

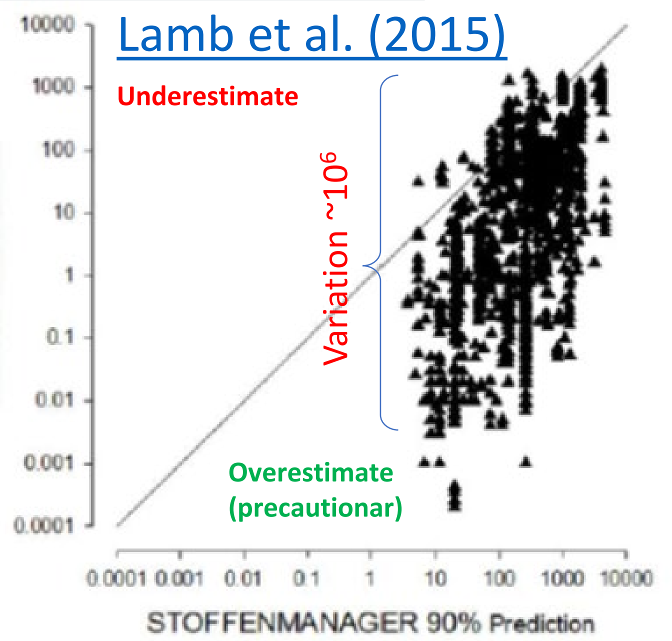
INTEGRANO

Regulatory compliance of ECHA R.14 models

Criteria	Stoffenmanager	Advanced REACH Tool (ART)
Scientific pedigree	**Not complied**: Koivisto et al. (2022), Based on subjective input variables, confidential subjective calibration factors that is used to calculate exposure by using multipliers. Model produces subjective outputs.	
ASTM D5157-97	**Not evaluated**	
Daubert criteria	**Not complied**: Koivisto et al. (2022)	
The Dutch Social Economic Council (Rijksoverheid)	**Not evaluated**	
Nicas et al. (2021)	**Not complied**: Koivisto et al. (2022)	

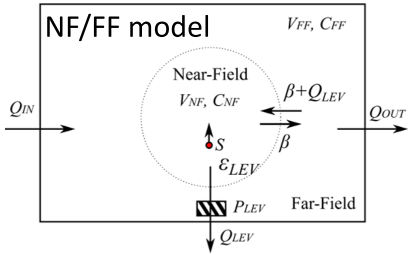
Scientific pedigree of other ECHA recommended tools theoretical backgrounds have not been evaluated (ECETOC TRA, MEASE 2.0, EMKG-EXPO-TOOL, BEAT)

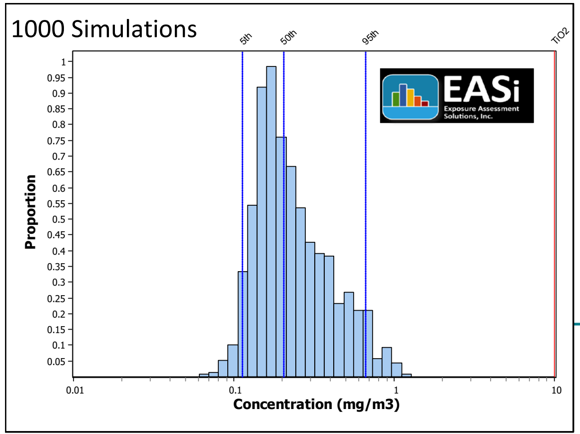




Funded by the European Union

Relevant exposure determinants for near-field (NF) exposure





Sensitivity test parameters (10 × change):

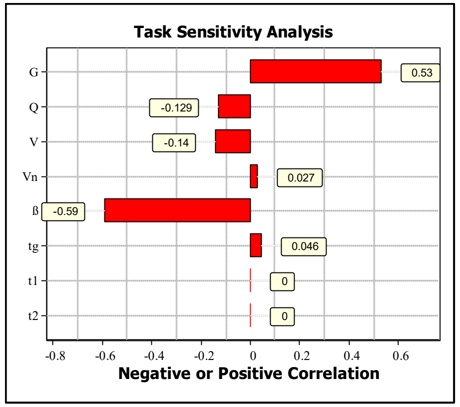
Emission rate (*G*): 1 to 10 mg/min

Air exchange ratio (*AER*): 1 to 10 1/h

Room volume (*V*): 200 to 2000 m^3

NF volume (V_n): 1 to 10 m^3

NF/FF air exchange (*ß*): 1 to 10 m^3/min



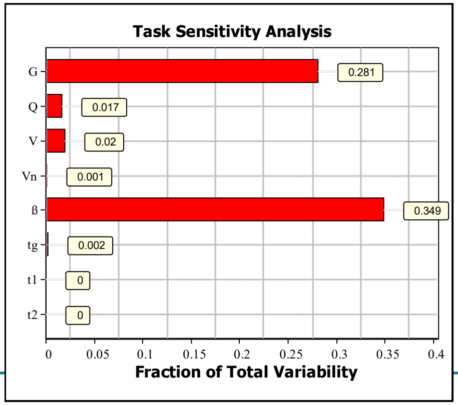
Emission rate

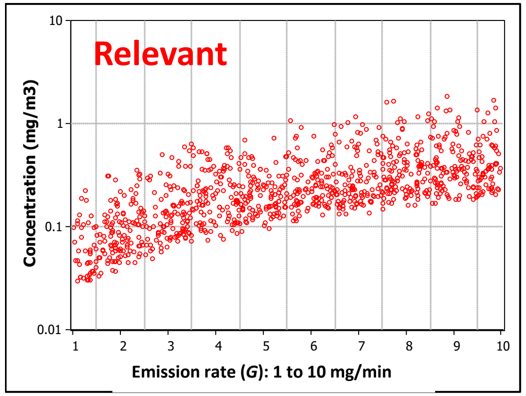
Air exchange ratio

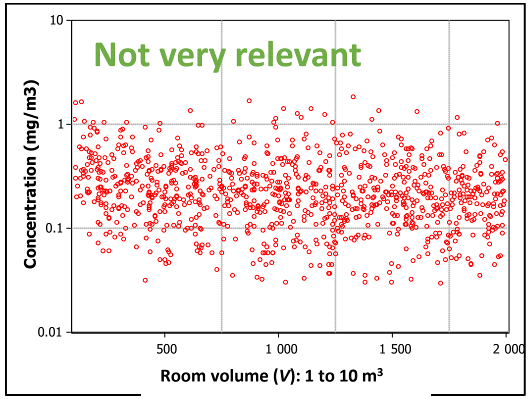
Room volume

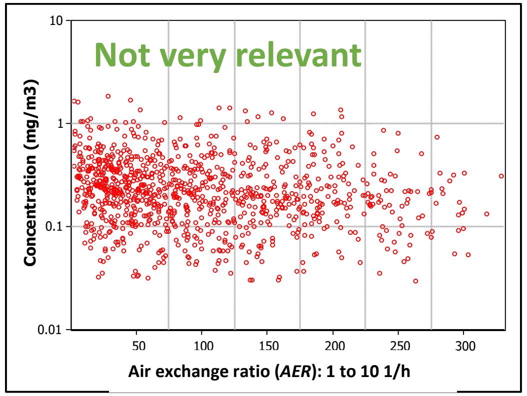
Near field volume

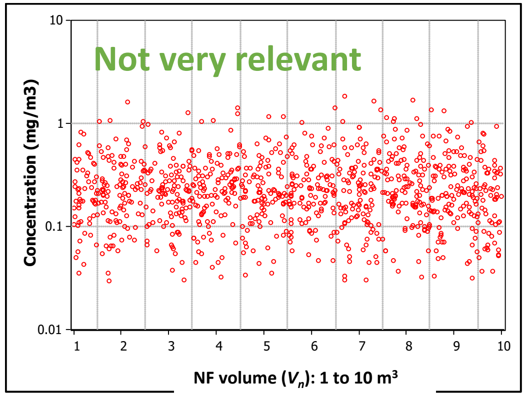
NF/FF air exchange ratio

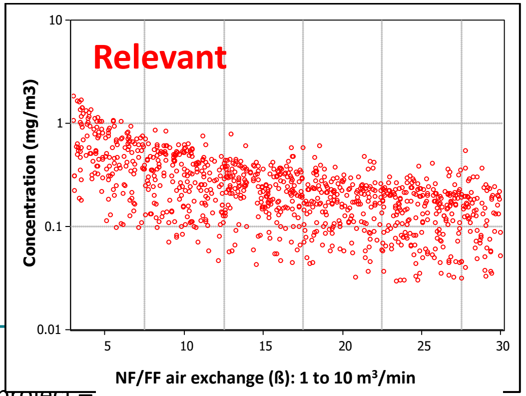












Realistic exposure assessment requires information on emissions and air mixing

Some development requirements

Regulatory compliance:

- Independent particle emission measurements (e.g. chamber studies) associated to different operational conditions
  - E.g. Boelter et al. (2009) showed that welding emissions measured in chamber were ~10 times higher than observed in a real work setting
  - E.g. Hanh et al. (2024) showed that overspray concentrations are overestimated in ~50% of the cases by more than a factor of 100

Better understanding of model parametrization:

- Process emissions for particulate matter
- Air mixing (ß in NF/FF model) conditions in different work settings

Summary 1/2

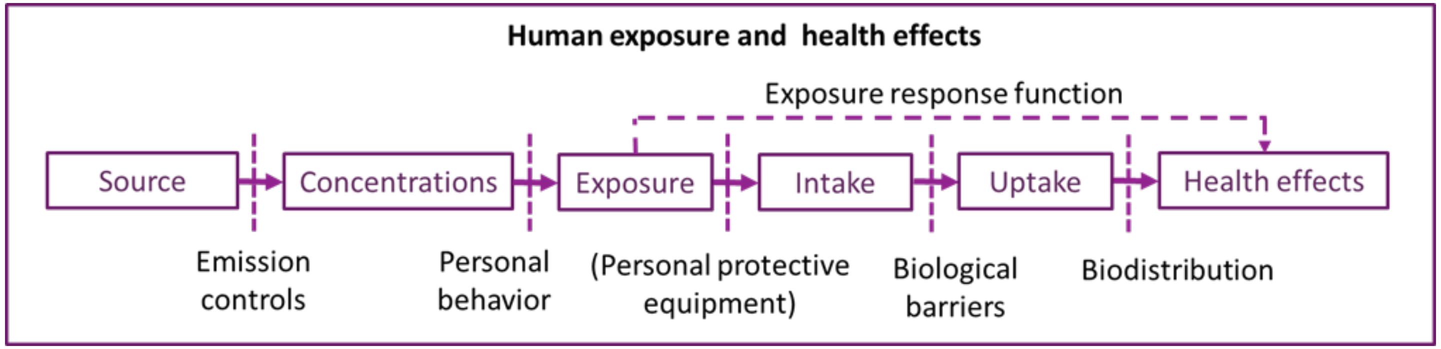
- **Applications of workplace measurements:**
  - Regulatory exposure compliance
  - Constitution of SEGs:
    - Reduce frequency of personal measurements
    - Predict exposures in another factory with similar OCs
  - Exposure model testing
- **Applications of exposure models:**
  - Regulatory exposure compliance in different OCs (EN689)
  - Setting safe conditions of use (CoU)
  - Optimizing exposure controls (designing efficient mitigation)
  - Derive priorities for measurements

Funded by
the European Union

Summary 2/2

- Process emissions are point of departure for exposure and health effects

  → Fundamental requirement for predictive exposure assessment



- NF/FF model for volatiles complies with regulatory criteria
  - Properly parametrized mass balance model is applicable for chemical safety decision making
- Modelling of particle emissions require better evaluation
- Better characterization of
  - Particle emissions
  - Air mixing (dilution)

Mass-balance based models have similar structures (box models) because all are based on the same physical law of conservation of mass (Ott, 1999)

Reminder: Models developed outside of the agency must meet the same acceptability and application criteria as models developed within EPA (NRC, 2007)