



MARKOPOLO

Noise and/or ultrafine particulate matter induced cerebral and cardiovascular damage: novel insights from experimental and epidemiological brain-heart axis biomarkers and computational models

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D21.9 Cluster joint policy brief 1

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Projects

Project name	Partner name
ClimAir	IDENER, EADS, SAS
ENACT	BRIDG-OU, UDIT, AIOTI, OKEY
ENVESOME	AUTH, AU
EXPOSIGNALZ	INSERM
EXPOSIM	KULEUVEN
MARKOPOLO	UMC Mainz, UNIPD, MUSC, VMU, MFUB, MFUB-VINS, CYI, concentris, M-PIC, LNS, LIH, UEF, JMU, SDU, DCS, SWISS-TPH
UPRISE	IISLAFE

List of Abbreviations

ABBREVIATION	DEFINITION
AAQD	Ambient Air Quality Directive (Directive (EU) 2024/2881)
AD	Alzheimer's disease
ADHD	Attention deficit hyperactivity disorder
AI	Artificial intelligence
AON / AONs	Adverse Outcome Network(s)
AOP / AOPs	Adverse Outcome Pathway(s)
APOE	Apolipoprotein E (gene)
AR	Allergic rhinitis
A β	Amyloid beta
CAD	Coronary artery disease
CAQI	Common Air Quality Index
CEI	Cumulative Exposure Index
CEN/TS	European Committee for Standardization Technical Specification
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular disease
DG ENV	Directorate-General for Environment, European Commission
DG RTD	Directorate-General for Research and Innovation, European Commission
DG SANTE	Directorate-General for Health and Food Safety, European Commission
DNA	Deoxyribonucleic acid
ECHA	European Chemicals Agency
EEA	European Environment Agency
EFSA	European Food Safety Authority
EHDS	European Health Data Space
EHN	ExpoHealthNet
ENVI	Committee on the Environment, Public Health and Food Safety, European Parliament
EU	European Union
EUR	Euro
EURION	European cluster on endocrine disruptor testing methods

EXPANSE	Exposome Powered Tools for Healthy Living in Urban Settings (Horizon 2020 project)
GBD	Global Burden of Disease (study)
HBM4EU	European Human Biomonitoring Initiative
HR	Hazard ratio
iPSC	Induced pluripotent stem cell
IT	Immunotoxicity
IUGR	Intrauterine growth restriction
IVIVE	In vitro to in vivo extrapolation
LBW	Low birth weight
MHD	Mental health disorders
MI	Myocardial infarction
MNPs	Micro- and nanoplastics
NAMs	New Approach Methodologies
NCDs	Non-communicable diseases
NGRA	Next-Generation Risk Assessment
NO ₂	Nitrogen dioxide
O ₃	Ozone
OR	Odds ratio
P-Tau	Phosphorylated tau protein
PARC	Partnership for the Assessment of Risks from Chemicals
PBK	Physiologically based kinetic (modelling)
PCBs	Polychlorinated biphenyls
PFAS	Per- and polyfluoroalkyl substances
PM	Particulate matter
PM _{2.5}	Particulate matter with a diameter of 2.5 µm or less
PNC	Particle number concentration
PoPs	Persistent organic pollutants
PTB	Preterm birth
RD	Respiratory disease
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RNA-seq	RNA sequencing
RR	Relative risk
SD	Sleep disorders
SDG	Sustainable Development Goal
SES	Socio-economic status
SGA	Small for gestational age
TFEU	Treaty on the Functioning of the European Union
UFPs	Ultrafine particles
WG1	Working Group 1 (ExpoHealthNet)
WHO	World Health Organization



ExpoHealthNet Policy Brief No. 1: Closing the Ultrafine Particle Gap

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Executive Summary

Air pollution remains Europe's largest environmental health risk. Current EU legislation does not regulate ultrafine particles (UFPs), the smallest and potentially most harmful fraction of airborne pollution. New evidence from the ExpoHealthNet cluster links UFP exposure alone to an estimated 419,000 new cardiovascular disease cases per year in the EU, and to an estimated mortality density of 35.7 deaths per 100,000 people per year in Europe (the latter from work currently under revision at *Cardiovascular Research*).

This document is Deliverable D9.8 Joint Policy Briefs I of the ExpoHealthNet cluster. It presents the first joint policy brief produced by Working Group 1, addressed to the review of EU air quality standards under Article 3 of the Ambient Air Quality Directive (AAQD, Directive (EU) 2024/2881). Article 3 requires the Commission to review the scientific evidence underpinning the standards by 31 December 2030, and every five years thereafter, and more frequently where substantial new scientific findings point to the need for it. The UFP evidence published by cluster partners in 2025 and 2026 is precisely the kind of finding that clause was designed to accommodate.

Two earlier milestones define the window in which the technical groundwork has to be laid. Member States must transpose the Directive by 11 December 2026, when the new monitoring regime, including mandatory UFP measurement at supersites, takes effect. Under Article 19, Member States must establish air quality roadmaps by 31 December 2028 where the 2030 limit or target values are at risk of not being met. Decisions taken in that period, on what is measured, reported and modelled, will determine what evidence is available to the Article 3 review.

The brief is addressed to the European Commission DG ENV, the European Environment Agency, EU Member State environment ministries, and the European Parliament ENVI Committee. Four policy options are presented, each with three tiers of ambition, all legally grounded in the existing AAQD framework and in Article 192 TFEU, and none requiring Treaty change. The deliverable also documents the WG1 working method and science-to-policy approach that underpins the choice of target, structure and content of the brief, so that it can be reapplied to the subsequent joint policy briefs.

1. Introduction

1.1 About this deliverable

This document is Deliverable Joint Policy Briefs I of the ExpoHealthNet (EHN) cluster, funded under Horizon Europe call HORIZON-HLTH-2024-ENVHLTH-02-06. It fulfils the commitment to produce at least three joint policy briefs over the lifetime of the cluster, with this first brief due at month 18 (M18).

It builds directly on the deliverable on the Cluster Policy Strategy, December 2025, which established the overall science-to-policy framework, selected priority EU legislative windows, and defined the methodology for translating cluster evidence into actionable policy recommendations.

1.2 The first policy brief: scope and target

The first EHN joint policy brief targets the review of EU air quality standards under Article 3 of the Ambient Air Quality Directive (AAQD, Directive (EU) 2024/2881). Article 3 requires the Commission to review the scientific evidence on air pollutants and their effects on human health and the environment by 31 December 2030, and every five years thereafter, and more frequently where substantial new scientific findings, such as revised WHO Air Quality Guidelines, point to the need for it. This is the first scheduled opportunity in the EU legislative calendar to:

- Introduce a regulatory framework for ultrafine particles (UFPs), which remain entirely unregulated despite compelling evidence of harm. Whereas Euro 6 and Euro VI regulate UFP emission from vehicles, they do not regulate UFP air quality legal limits.
- Legislate a binding trajectory to full alignment with the WHO 2021 PM_{2.5} Air Quality Guideline of 5 micrograms per cubic metre.
- Introduce a Cumulative Exposure Index (CEI), complementing the established Common Air Quality Index (CAQI), to capture the cumulative health burden of multiple pollutants and stressors acting simultaneously; and
- Formally recognise Next-Generation Risk Assessment (NGRA) evidence in limit-setting where epidemiological data remain heterogeneous.

The cluster position is that the UFP evidence generated in 2025 and 2026 meets the threshold of substantial new scientific findings set out in Article 3(1), and that the review should therefore be brought forward rather than left to the outer 2030 deadline. Independently of that timing, the preparatory phase runs through the transposition deadline of 11 December 2026 and the Article 19 air quality roadmaps of 31 December 2028, which is when Member States decide what they monitor and report.

This policy window was identified as the priority target because the EHN cluster evidence is positioned to address gaps that the 2024 revision of the AAQD could not resolve for lack of a sufficient evidence base at the time.

1.3 Primary and secondary audiences

Table 1 Primary and secondary audiences

Audience	Role in the review process
European Commission DG ENV (primary)	Leads the review process and drafts any legislative proposal
European Environment Agency (primary)	Provides technical assessment supporting the Commission review
EU Member State environment ministries (primary)	Must transpose and implement the revised AAQD; influence Council positions
European Parliament ENVI Committee (secondary)	Co-legislator; shapes political ambition for any subsequent revision
DG SANTE (secondary)	Links AAQD reform to EU health strategy and NCD prevention frameworks
WHO Europe (secondary)	Provides scientific anchoring for guideline values and health targets

1.4 Objectives

This deliverable has three objectives:

- To present the first joint policy brief produced by the EHN cluster (see Annex), to be submitted as a practical evidence document that supports policymakers in the review of EU air quality standards under Article 3 of the AAQD.
- To document the WG1 methodology and science-to-policy approach that underpins the choice of target, structure, and content of the brief; and
- To provide a replicable template and process description that will guide the production of the second (M48) and third (M60) policy briefs.

2. Context: WG1 Approach and Methodology

2.1 WG1 working method

Working Group 1 (WG1) of the ExpoHealthNet cluster is responsible for science translation for policy and practice. It is co-led by MARKOPOLO (Andreas Daiber, UMC Mainz) and ENACT (Maria Eugenia (Xenia) BELTRÁN JAUNSARÁS, BRIDG-OU) and brings together policy-science liaison representatives from all seven partner consortia.

WG1 held its first full meeting in May 2025, followed by a session in July 2025, an in-person meeting in Barcelona in September 2025, and bimonthly online meetings thereafter. The approach to the first policy brief was developed iteratively across these meetings, with the March 2026 session consolidating the final strategy.

2.2 How WG1 selected the target directive and policy window

The selection of the AAQD review as the primary target followed a structured screening process evaluating potential legislative windows against four criteria:

- Scientific readiness: does the cluster already hold, or will it hold by M18, peer-reviewed evidence that is directly actionable for this decision?
- Policy timing: is the legislative window open or opening within the deliverable period, so that the brief can influence rather than merely document?
- Decision type alignment: does the policy window require the type of decision (limit values, monitoring, mixture assessment) for which cluster evidence is most directly relevant?
- Institutional access: EHN aims at engaging with the relevant decision-maker through existing stakeholder relationships.

In this context the AAQD review scored strongly on all four criteria. The review clause in Article 3 of Directive (EU) 2024/2881 places a binding obligation on the Commission to review the scientific evidence underpinning the air quality standards by 31 December 2030, and more frequently where substantial new scientific findings point to the need for it, assessing whether the standards remain appropriate and whether additional pollutants should be covered.

This is a decision of exactly the type for which cluster evidence is most directly relevant: limit values, monitoring requirements and mixture assessment. MARKOPOLO publications of 2025 and 2026 quantifying the cardiovascular burden attributable to UFPs meet the scientific readiness criterion and constitute the class of finding the anticipation clause was designed to accommodate.

The intervening implementation milestones, transposition by 11 December 2026 and the Article 19 air quality roadmaps by 31 December 2028, provide concrete entry points at which cluster evidence can shape monitoring and reporting practice before any legislative proposal is drafted. It is expected that UFP regulation and alignment with the WHO PM2.5 guideline are potential topics for the AAQD review.

2.3 Briefs by decision type, not pollutant category

A central methodological choice in the EHN approach is to structure policy briefs around the type of regulatory decision to be made, rather than around individual pollutants or stressors. WG1 identified seven decision categories that frame the cluster portfolio of policy briefs:

Table II Decision Categories

Decision category	Policy instrument focus	EHN evidence link
D1 - Setting and updating limit values	Numerical standards; WHO alignment; phased trajectories	UFP burden data; PM _{2.5} epidemiology; NGRA
D2 - Monitoring and surveillance	Sampling protocols; biomonitoring; supersites	High-resolution exposure mapping; PNC methodology
D3 - Mixture risk assessment	Cumulative indices; synergistic exposure models	Multi-exposure cohort data; CEI methodology
D4 - Vulnerable group protections	Prenatal windows; children; low-SES populations	UPRISE birth outcomes; EXPOSIGNALZ neurodevelopment
D5 - Urban planning and mobility co-benefits	Green infrastructure; zero-emission zones	EXPOSIGNALZ Sweden mitigation studies
D6 - Hazardous waste and circularity	Safe-by-design; recycled material safety	ENVESOME; EXPOSIM chemical mixture evidence
D7 - Clinical prevention integration	Exposome-informed NCD prevention; health system linkage	ENACT risk prediction models; MARKOPOLO CVD

This first policy brief primarily addresses D1 (limit values) and D3 (mixture risk assessment), with supporting evidence for D4 (vulnerable groups).

2.4 The five-part evidence-to-action structure

Each EHN policy brief follows a standard five-part evidence-to-action structure:

Table III evidence-to-action structure

Module	Content	Purpose
A: Evidence	Two to four key findings from cluster research, translated into plain language with quantitative estimates (hazard ratio, odds ratio, relative risk, attributable burden) and with the maturity rung of each claim identified	Establishes the scientific case for action and makes the strength of that case explicit
B: The gap	The specific silence, inconsistency, or outdated assumption in existing law that the evidence exposes	Links science to the specific policy deficiency
C: Options	Three tiers per option (minimal, moderate, transformative), all legally grounded	Gives the decision-maker genuine choices
D: Feasibility	Legal basis, institutional actors, subsidiarity considerations, costs and constraints	Ensures recommendations are actionable
E: Recommendation	One clear sentence per actor, time-bound and specific	Ensures the brief can be acted on immediately

WG1 also applies a five-rung science maturity ladder to characterise the strength of the evidence behind each policy claim, assessing:

1. Signals: Early or isolated evidence of an effect not yet replicated.
2. Supported epidemiology association in non-communicable diseases: Consistent epidemiological association across independent cohorts or populations.
3. Mechanistic plausibility: A biological pathway anchored in multi-omics data, Adverse Outcome Pathways (AOPs) and Adverse Outcome Networks (AONs), and in vitro to in vivo extrapolation (IVIVE) or physiologically based kinetic (PBK) modelling.
4. Actionable threshold or indicator: A quantified exposure-response function, attributable burden estimate or measurable indicator that a regulator can apply.
5. Implementable measure. A policy option with an identified legal basis, an enforcement pathway and a cost-benefit case.

The ladder is applied below to the five key messages of the first brief. Making the assessment explicit serves two purposes: it shows which claims are ready to support a regulatory ask and which are not yet, and it identifies the evidence that the cluster still needs to generate before the Article 3 review.

Table IV Evidence maturity of the key messages in the first policy brief

Key message (Annex)	Core claim	Rung reached	Evidence base at that rung	What is needed for the next rung
KM1. UFPs are the largest un-addressed air-pollution gap in EU law	UFPs are monitored at supersites under Article 10 but carry no limit value, target value or exposure reduction obligation, and their burden is comparable to regulated pollutants	4 Actionable indicators	The regulatory gap is a matter of documented law. The comparative burden claim rests on the attributable-burden estimates behind KM2	An agreed exposure-response function for particle number concentration, and an EEA-endorsed feasibility assessment for a PNC metric
KM2. The health burden is quantified and large	419,000 UFP-attributable CVD cases per year in the EU; 35.7 deaths per 100,000 per year in Europe; 1.99 million excess deaths globally	4 Actionable indicators	Burden estimates derived from cohort hazard ratios applied to GBD data and to global exposure fields; mechanistic support at rung 3 from animal and human work on endothelial dysfunction and oxidative stress	Publication of the mortality estimate (currently under revision); replication of the hazard ratios in additional European cohorts; harmonised uncertainty reporting across the three estimates
KM3. The EU 2030 PM2.5 limit is still double the WHO guideline	A legal pathway to 5 µg/m ³ should be embedded rather than deferred	5 Implementable measures	WHO 2021 guideline value; extensive European epidemiology showing effects below 10 µg/m ³ ; Commission impact assessment quantifying net benefits of EUR 29 to 38 billion across alignment scenarios; Article 7 AAQD provides the instrument	None for the evidence. The remaining constraint is political feasibility of the phase-in trajectory
KM4. Single-pollutant limits underestimate real-world risk	Combined exposure to particles, NO ₂ , noise and chemical mixtures produce effects no individual limit captures	3 Mechanistic plausibility	Consistent associations from multi-exposure cohorts covering air pollution, noise and greenness; multi-omics and Adverse Outcome Network evidence from ENVESOME, EXPOSIM and MARKOPOLO on shared oxidative stress and inflammatory pathways	A validated cumulative exposure-response function, and a tested index specification with reference values. This is the purpose of the CEI work in Option C and the principal evidence gap for D9.9
KM5. Four legally feasible options, each in three tiers	All options are anchored in the existing AAQD framework and Article 192 TFEU; none requires Treaty change	5 for the legal framing; individual options inherit the rung of their evidence	Legal basis mapped article by article in Section 6 of the brief, with lead actors and constraints identified	Options A and B are supported at rungs 4 to 5 and are ready now. Options C and D rest on rung 3 evidence and are framed accordingly, as methodology development rather than immediate limit-setting

Key Message 4 (KM4) is the least mature and is deliberately framed as a structural argument about how limits are set, rather than as a numerical claim, because a validated cumulative exposure-response function does not yet exist.

2.5 Stakeholder engagement and advisory input

WG1 operates with a policy advisory board. Dr Gerardo Sanchez of the European Environment Agency is the confirmed adviser, engaged since October 2025. The advisory board is being expanded with two to three additional advisers nominated by the partner consortia. Prior to finalising this brief, WG1 consulted DG RTD and the EEA regarding expected topics and submission format for the AAQD 2028 to 2030 review process.

3. Policy Context: The Article 3 Review and the Road to 2030

3.1 Why the 2028 review matters

Directive (EU) 2024/2881 entered into force on 10 December 2024 and sets air quality standards to be attained by 1 January 2030. Three provisions define the policy window for this brief.

Transposition, 11 December 2026 (Article 31). Member States must bring into force the national laws, regulations and administrative provisions needed to comply with the Directive. Directives 2004/107/EC and 2008/50/EC are repealed with effect from 12 December 2026. From this point the new assessment regime applies, including mandatory monitoring of ultrafine particles, black carbon and ammonia at supersites under Article 10.

Air quality plans and roadmaps, 31 December 2028 (Article 19). Where levels between 2026 and 2029 exceed the values to be attained by 2030, Member States must establish air quality roadmaps setting out measures to secure compliance, and air quality plans where limit or target values are already exceeded. This is a Member State obligation, not a revision of the Directive, but it determines what is measured, modelled and reported in the years immediately preceding the Commission review.

Review of the standards, 31 December 2030 (Article 3). The Commission must review the scientific evidence on air pollutants and their health and environmental effects by 31 December 2030, and every five years thereafter, and more frequently where substantial new scientific findings, such as revised WHO Air Quality Guidelines, point to the need for it. The review must assess whether the standards remain appropriate, whether additional pollutants should be covered, and what options and timelines exist for alignment with the most recent WHO guidelines.

The cluster addresses all three. The substantive asks in the brief are directed at the Article 3 review; the near-term actions are directed at the transposition and roadmap phases, where they can be implemented without legislative change.

3.2 The five open issues identified by WG1

Table V open issues identified by WG1

Issue	Status heading into the Article 3 review
UFPs: no limit value, no monitoring obligation beyond supersites, no indicative target	Unresolved gap - no legal basis
PM _{2.5} : 2030 target of 10 micrograms per cubic metre is double the WHO 2021 guideline of 5 micrograms per cubic metre	Partially resolved - WHO alignment pending
Mixture exposure: no mechanism to account for combined or synergistic multi-pollutant burden	Unresolved gap - no legal mechanism
Compliance: postponement of attainment deadlines permitted up to 1 January 2040 under Article 18; compensation rights for breaches of Articles 19 and 20 untested	Implementation risk - monitoring required
Health scope: dementia, neurodevelopmental outcomes, and reproductive health not covered by AAQD impact assessments	Partially resolved - scope expansion needed

The first policy brief concentrates on the first three issues, where the cluster evidence is strongest and the regulatory opportunity is clearest. Issues four and five will be addressed in subsequent policy briefs as additional cluster evidence matures.

3.3 The policy window timeline

Table VI The policy window timeline

Date	Milestone	EHN action
December 2026 <i>(considered initially, but short time)</i>	Transposition deadline (Article 31); Directives 2004/107/EC and 2008/50/EC repealed from 12 December 2026; new assessment regime applies, including mandatory UFP monitoring at supersites (Article 10)	Brief already with DG ENV, the EEA and Member State ministries; engage with implementing act consultations on supersite and PNC specifications
2026-2027	Pre-legislative window: EEA develops UFP monitoring protocol and CEI methodology	Provide technical evidence input; engage EEA advisory board; open the question of EHDS interoperability for the cluster cohorts with DG SANTE, so that exposure-linked data are available to the review.
2027	EEA technical assessment work and stakeholder consultations feeding the Article 3 review	Submit formal consultation response based on updated cluster evidence
31 December 2028	Deadline for Member State air quality roadmaps under Article 19; postponement notifications to the Commission by 31 January 2029	Offer harmonised PNC monitoring and cumulative-exposure indicators as inputs to national roadmaps

2029 to 2030	Commission conducts Article 3 review of the standards, due by 31 December 2030 and earlier where substantial new findings justify it; a legislative proposal is expected in 2029 to 2030 if the review concludes that revision is needed	Support the review with consolidated UFP, WHO alignment and CEI evidence; remain available for technical follow-up
2030	2030 limit and target values must be attained by 1 January 2030: Zero Pollution Action Plan target of at least 55% reduction in premature deaths from air pollution against 2005	Monitor compliance; feed into next review cycle

4. Key Evidence Informing the Brief

The policy brief in the Annex draws on three evidence pillars: quantified health burden, mechanistic confirmation, and socioeconomic cost of inaction (mirrored to the socioeconomic benefits of mitigation).

4.1 Hazard ratios and attributable burden for UFPs (MARKOPOLO)

The two burden estimates below rest on exposure datasets of different spatial resolution, produced in sequence by the same research group. The cardiovascular incidence estimate was derived from global exposure fields at 10 km resolution; the higher-resolution 1 km product described in the second bullet was released subsequently and underpins the mortality estimate and the urban concentration figures.

MARKOPOLO consortium - key quantitative findings:

- **UFP-attributable CVD incidence in the EU:** 419,000 new cases per year (95% CI: 78,000 to 712,000). Globally, the figure is 5.6 million new cases per year, equivalent to 11 to 12% of total global cardiovascular disease incidence. Hazard ratios from a large Dutch cohort applied to GBD incidence data and to global UFP exposure fields at 10 km resolution. (Kuntic et al., Redox Biology 2025)
- **High-resolution UFP exposure maps:** first global maps of particle number concentration at 1 km resolution, combining ground measurements with machine learning (XGBoost). Urban concentrations exceed 40,000 particles per cm³. (Georgiades et al., Scientific Data, 2025)
- **UFP mortality density in Europe:** 35.7 deaths per 100,000 per year (95% CI: 15.8 to 65.5). derived from the 1 km exposure product combined with hazard ratios from cohort studies in the United States, Canada and the Netherlands. (Lelieveld et al., Cardiovascular Research 2026.)
- **Global UFP excess mortality:** 1.99 million deaths per year (95% CI: 0.81 to 3.89 million). Combustion sources in cities are the primary driver. (Lelieveld et al., 2026)
- **Mitigation potential:** an annual limit value of 5,000 particles per cm³ could reduce global UFP-attributable excess mortality by about 45%. (Lelieveld et al., 2026)

4.2 Mechanistic insights (MARKOPOLO, ENVESOME)

Confirmed pathways supporting causal inference:

- **UFP nanoparticles (<250 nm)** cause endothelial dysfunction and elevated blood pressure via oxidative stress and systemic inflammation.
- **Short-term aircraft noise** induces a fundamental shift in heart proteome and metabolome bearing hallmarks of CVD (Marques et al., Science of the Total Environment 2025).
- **Trained innate immunity** links chronic pollution exposure to atherosclerosis progression; cumulative lifetime burden matters (Riksen et al., Nature Reviews Cardiology 2023).
- **Multi-omics evidence** confirms that co-exposure to phthalates and metals disrupts urea cycle and choline metabolism, linking mixture exposures to systemic harm (ENVESOME, Papaioannou et al., Environmental Research 2021).

4.3 Socioeconomic benefits of mitigation (EXPOSIGNALZ, MARKOPOLO)

Health economics evidence supporting the cost-benefit case for action:

- **Fossil fuel elimination:** phasing out all fossil fuel use could prevent 5.13 million global premature deaths per year (Lelieveld et al., BMJ 2023).
- **Sweden per-case avoided costs:** EUR 117,000 per stroke case, EUR 76,000 per MI case attributable to air pollution (Kriit et al., PLoS One 2024).
- **Dementia burden:** approximately 820 new dementia cases per year in Sweden attributable to PM_{2.5}, with a lifetime cost of approximately EUR 213,000 per case (Kriit et al., Environmental Health 2021).
- **EU-level benefit:** the Commission impact assessment estimated net economic benefits exceeding EUR 29 billion under partial WHO alignment and up to EUR 38 billion under full alignment.

5. Planned Future Policy Briefs

Table VII The Planned Future Policy Briefs

Deliverable	Target window	Anticipated focus	Delivery
Joint Policy Briefs II	To be confirmed (EU policy calendar 2026-2027)	Anticipated focus on the Environmental Noise Directive revision, occupational exposure regulation, or the EU Chemicals Strategy, depending on cluster evidence alignment at M48	Month 48
Joint Policy Briefs III	To be confirmed (EU policy calendar 2028-2029)	Anticipated focus on vulnerable groups, reproductive health, or clinical prevention integration, drawing on the full cluster evidence base available at project end	Month 60

The decision on topics will be made at the September/October 2026 in-person cluster meeting, following consultation with the policy advisory board and updated monitoring of the EU policy calendar.

6. Conclusion

D9.8 presents the first joint policy brief of the ExpoHealthNet cluster, addressed to the review of EU air quality standards under Article 3 of the Ambient Air Quality Directive. The brief is the product of a structured, evidence-driven process developed by WG1 over the first 18 months of the cluster, documented in this deliverable and in its predecessor.

The choice of target reflects both the strength of the cluster's available evidence and the structure of the regulatory calendar. Article 3 of the AAQD requires the Commission to review the air quality standards by 31 December 2030, and sooner where substantial new scientific findings justify it. This is the first legally scheduled opportunity to regulate ultrafine particles, to legislate a pathway to WHO PM_{2.5} alignment, and to introduce a mechanism for capturing cumulative multi-pollutant exposure burden. The preparatory phase, however, runs now: transposition by 11 December 2026 and the Article 19 air quality roadmaps by 31 December 2028 determine what evidence will be available when the review takes place. All three gaps are ones the cluster is positioned to address, and the cluster's own lifetime ends in December 2029, immediately before the Article 3 deadline.

The full policy brief is provided as the Annex to this deliverable. It is a self-contained document intended for direct use by the target audiences listed in Section 1.3 and is also available as a standalone output for wider dissemination. The brief is published in its designed layout as version 4.5 with a citable DOI (<https://doi.org/10.5281/zenodo.22200814>), which should be used when referencing the brief.

ANNEX

Closing the Ultrafine Particle Gap in EU Air Quality Law

Evidence and opinions for the 2028–2030 review of the Ambient Air Quality Directive

PREPARED BY

ExpoHealthNet (EHN) cluster: Working Group 1

POLICY WINDOW

AAQD 2028 review
(Commission proposal expected 2029–2030)

DECISION CATEGORIES

Setting/updating limit values (primary)
Mixture risk assessment (secondary)

HOW TO CITE

<https://doi.org/10.5281/zenodo.22200814> (2026)

PRIMARY AUDIENCE

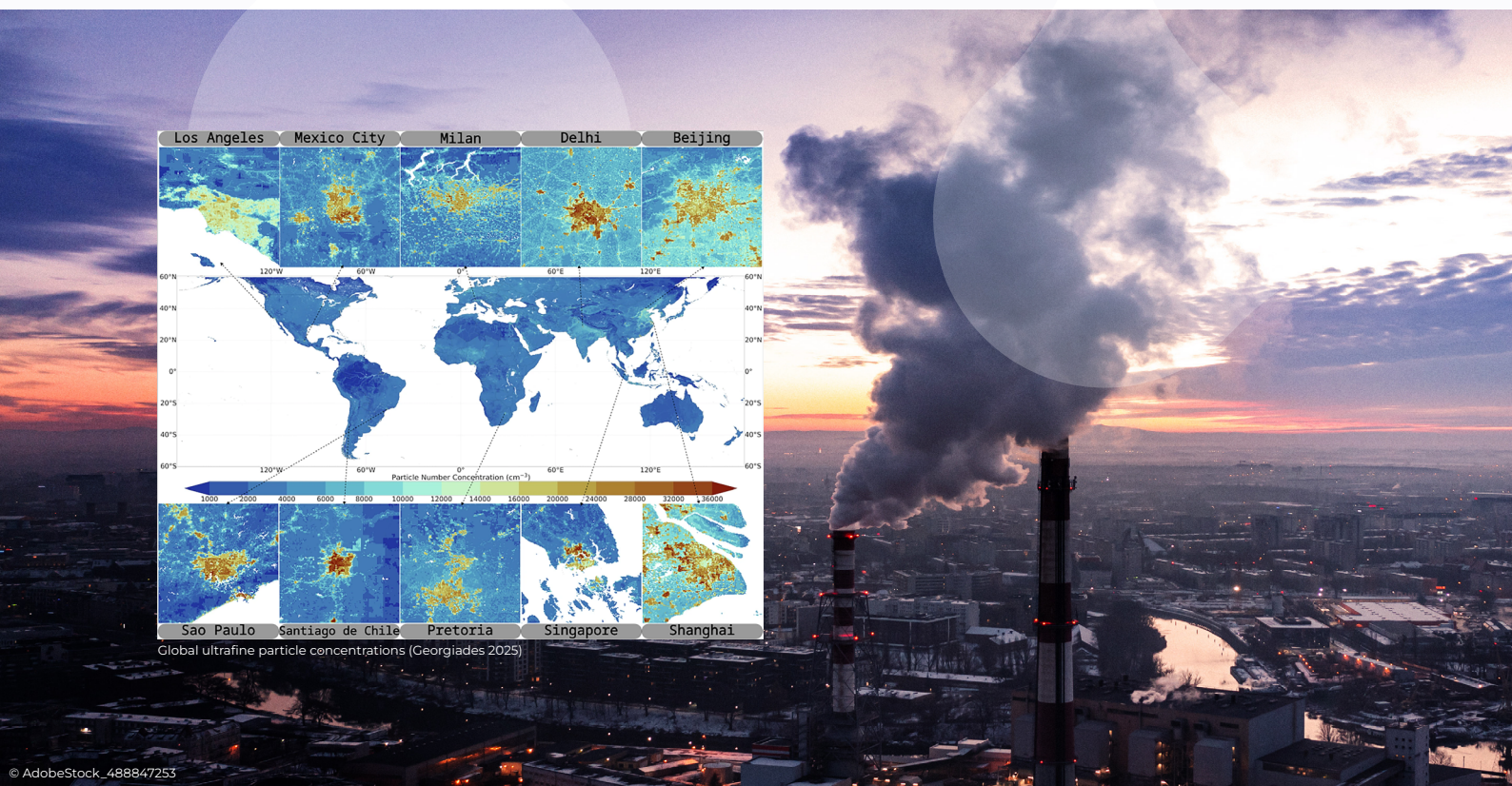
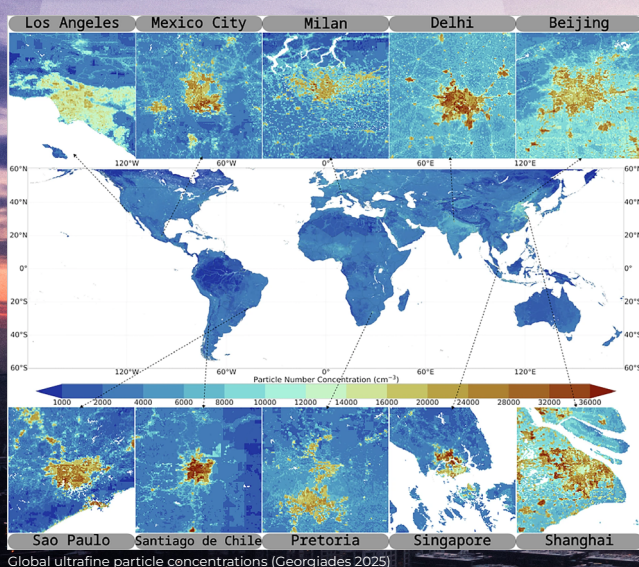
European Commission DG ENV;
European Environment Agency;
EU Member State environment ministries

SECONDARY AUDIENCE

European Parliament ENVI Committee;
DG SANTE; WHO Europe

EVIDENCE SOURCE

EHN partner cohort studies;
EEA reports 2024–2025;
peer-reviewed publications 2024–2026



KEY MESSAGES FOR POLICYMAKERS

- 1. Ultrafine particles (UFPs) are the largest unaddressed air-pollution gap in EU law.** Under [Directive \(EU\) 2024/2881](#), UFPs are now monitored at supersites, but no binding limit value, target value, or exposure reduction obligation exists. The 2028–2030 review is the first opportunity to close this gap.
- 2. The health burden is quantified and large.** New ExpoHealthNet evidence attributes approximately 419,000 new cardiovascular disease cases per year [1]. This burden is comparable to several pollutants already covered by limit values, driven by particle number concentrations of over 40,000 particles per cm³ in major cities [2]. A parallel finding from large-scale atmospheric modelling estimates 1.99 million excess deaths globally and 35.7 deaths per 100,000 population in Europe each year attributable to UFP exposure [3]. Current EU air quality limits are not designed to address this burden, despite UFPs being the smallest and potentially most harmful fraction of airborne pollution [4].
- 3. The EU 2030 PM_{2.5} limit (10 µg/m³) is still double the WHO guideline (5 µg/m³).** The 2028–2030 review must embed a legal pathway to WHO alignment, not defer it indefinitely.
- 4. Single-pollutant limits underestimate real-world risk.** The evidence shows that combined exposure to particles, NO₂, noise and chemical mixtures produces synergistic effects on cardiovascular, respiratory, neurodegenerative and reproductive outcomes that no individual limit captures.
- 5. Four concrete, legally feasible options** are presented in Section 4, each in three tiers of ambition. All are anchored in the existing AAQD framework and TFEU Article 192; none requires treaty change.

The numbers at a glance, also summarized in Figure 1

239,000	419,000	1.99 M	>40,000
EU premature deaths/year (PM_{2.5})	EU new CVD cases/year from UFPs	Global premature deaths/year from UFPs	UFP particles/cm³ in major cities
<i>EEA, 2024</i>	<i>Kuntic et al., 2025</i>	<i>Lelieveld et al., 2026</i>	<i>Georgiades et al., 2025</i>

Ultrafine Particles in Europe 2026 - summary for policymakers

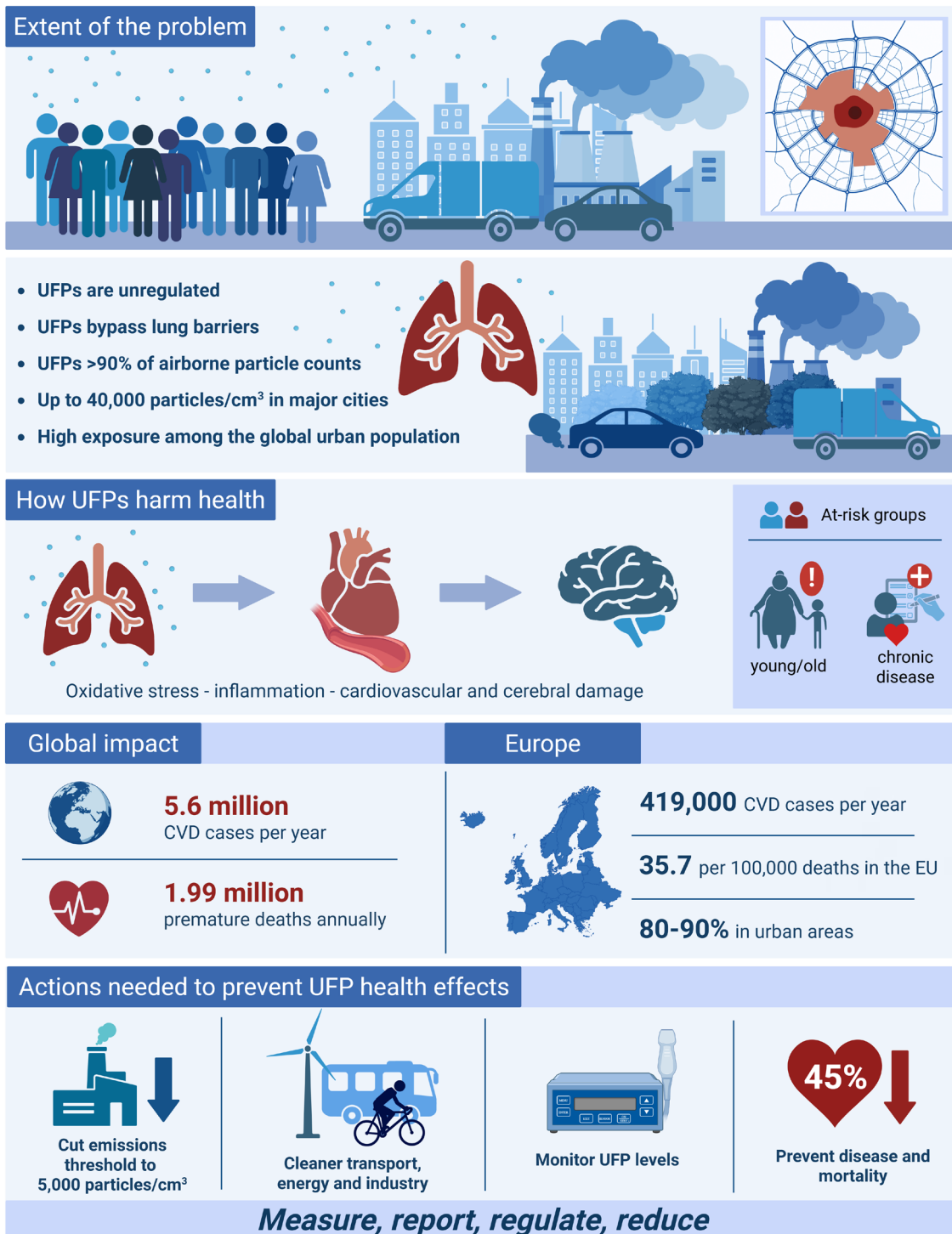


Figure 1. The scale of UFP health effects at a glance: (1) extent of the problem; (2) how UFPs harm health; (3) health impacts, in Europe and globally; (4) actions needed to prevent UFP health effects. Generated using biorender.com.

1 THE PROBLEM

Why Current Limits Are Not Protecting the Population's Health

1.1 What the AAQD directive currently says

The revised Ambient Air Quality Directive (AAQD, 2022/0347 and 2024/2881) repeals and replaces the 2004 and 2008 directives from December 2026. It sets binding annual mean limits for thirteen pollutants [5]. For the two most health-relevant pollutants, the fine particulate matter (PM_{2.5}) and nitrogen dioxide (NO₂); the current EU legal limits, with a certain flexibility for national authorities to adjust, are:

- PM_{2.5}: 10 µg/m³ by 2030 (down from 25 µg/m³ under the previous directive)
- NO₂: 20 µg/m³ by 2030 (down from 40 µg/m³)

These regulations represent significant progress. However, the World Health Organisation's updated Air Quality Guidelines (2021) recommend a PM_{2.5} level of 5 µg/m³ (half the current EU 2030 target) [6]. The evidence base behind the WHO guidelines includes extensive European epidemiological data showing health effects well below 10 µg/m³. Over 90% of the EU urban population is currently exposed to PM_{2.5} concentrations above the WHO guideline ([EEA, 2026](#)). This is the basis of Key Message 3. It should also be noted that the European Commission's impact assessment report accompanying the proposal of the new AAQD estimated substantial net economic benefits across all policy scenarios, exceeding €29 billion under partial alignment, €36 billion under closer alignment, and €38 billion under full alignment with the 2021 WHO Air Quality Guidelines.

1.2 What current limits do not cover

Four structural gaps in the current AAQD are exposed by the latest cohort and mechanistic evidence; these gaps underpin Key Messages 1 and 4:

- **Ultrafine particles (UFPs, diameter < 100 nm):** UFPs are now subject to mandatory monitoring at supersites under Article 10 of Directive (EU) 2024/2881, but no binding limit value, target value, exposure reduction obligation or alert threshold exists. UFPs make up around 91% of all airborne particle count close to combustion sources. Because of their tiny size, they bypass respiratory defences, enter the bloodstream, and reach internal organs, including the brain and heart; affecting up to 45% of the global population, especially the share living in larger cities [7].
- **Mixture exposure:** the directive sets limits for each pollutant independently. A person who is simultaneously exposed to PM_{2.5}, NO₂, traffic noise, and night-time light carries a cumulative health burden that no single limit is designed to capture. Cumulative-exposure models consistently yield higher attributable-burden estimates than single-pollutant models.
- **Sensitive life stages:** annual mean limits do not efficiently differentiate by developmental stage. Prenatal exposure to pollutants (including UFPs), together with co-occurring chemical and physical stressors, is associated with adverse birth outcomes (preterm birth, intrauterine growth restriction) and neurodevelopmental effects whose clinical manifestation may be delayed by years or decades (UPRISE, EXPOSIGNALZ evidence base). The AAQD's annual-mean architecture cannot detect short-term exceedances during these critical windows, and no mechanism currently requires Member States to report life-stage-resolved exposure.
- **Vulnerable population subgroups:** patients with pre-established chronic disease, and individuals with higher genetic susceptibility [8] (e.g. carriers of the APOE ε4 allele) , are more susceptible to the adverse effects of air pollution [9] and to the additive effects of other regulated toxic chemicals such as highly chlorinated PCBs [10]. Multi-omics biomarkers (genome-wide DNA methylation, microRNA profiling from extracellular vesicles, transcriptomic, proteomic and metabolomic signatures) developed in the ENVESOME, EXPOSIM and MARKOPOLO consortia now make it feasible to characterise these susceptibility strata at the population level and to support population-stratified limit-setting.

2 THE EVIDENCE

Three new key findings (also summarized in Figure 1)

2.1 Ultrafine particles cause cardiovascular harm at a global scale

2025/2026 studies by researchers in the MARKOPOLO consortium combined animal experiments, human exposure data, and global atmospheric modelling to quantify the cardiovascular burden of UFP exposure. The findings below substantiate Key Message 2.

Key finding 1: Cardiovascular disease burden from UFPs

- UFP is estimated **to cause 419,000 new cardiovascular disease cases every year in the EU**. Globally, the figure is **5.6 million new cases per year, equivalent to 11 to 12% of total global cardiovascular disease incidence** [1]. These are cases that would not occur in the absence of UFP pollution. Mechanistically, air pollution exposure has been shown to impair endothelial function and increase blood pressure, key pathways in cardiovascular disease development [11].
- *Method: The incident CVD and population data have been adopted from the Global Burden of Disease (GBD) study [12] and the attributable fraction has been derived from the hazard ratio (HR) associated with exposure to UFP from data of a published large Dutch cohort study [13].*

2.2 High-resolution global maps reveal who is exposed, and where

First global maps of UFP concentrations at 1-kilometre resolution were produced using a combination of ground measurements and machine-learning modelling [2], while accounting for limitations in particle-count estimations, e.g. agglomerate formation.

Key finding 2: UFP exposure mapping

- UFP concentrations vary dramatically by location: from a few thousand particles/cm³ in rural areas to over **40,000 particles/cm³ in major cities** [2]. Note that this represents annual average exposure, while local conditions, for example, near dense traffic routes, can even be much higher with peak values >100,000 particles/cm³ [14]. In summary, we reliably predict UFP and total particle number concentrations (PNCs), consistent with measured ranges in numerous countries (up to 26,600 particles/cm³), with the highest accuracy in Europe [15, 16]. With UFPs, on average, accounting for 91% of all airborne particle counts, these new data provide the foundation for the first robust European exposure assessments for this pollutant class.

2.3 Mortality burden from UFPs is comparable to regulated pollutants

A further analysis, combining the global UFP exposure maps with hazard ratios from epidemiological cohort studies, estimates the mortality attributable to UFP exposure across Europe and North America. The mechanistic pathway from UFP deposition through systemic inflammation, oxidative stress and endothelial dysfunction to cardiovascular and neurodegenerative outcomes is now mapped in Adverse Outcome Network (AON) frameworks [8, 17], providing a mechanistic basis for setting limit values where epidemiological exposure-response data remain heterogeneous. A burden comparable to that of regulated pollutants, from an exposure with no limit value, is the core of Key Message 1.

Key finding 3: Mortality attributable to UFPs

- The estimated annual mortality density attributable to UFP exposure in **Europe is 35.7 deaths per 100,000 people**. Globally, an **estimated 1.99 million people die prematurely each year** due to UFP pollution [3]. An annual air quality limit of 5,000 particles/cm³ could reduce global excess mortality by about 45%. The combustion sources in cities (traffic, energy production, and industry), should be the priority for intervention. PM_{2.5} regulation addresses these sources but does not target specific UFP regulations. UFPs can still be abundant even when PM_{2.5} is low.
- *Method: The baseline mortality and population data have been adopted from the GBD study [12]. The attributable fraction has been derived from the hazard ratio (HR) associated with all-cause (non-accidental) mortality, assuming it represents the relative risk (RR) associated with the exposure to UFP from cohort studies in the USA, Canada, and the Netherlands, representing in total 13.3 million participants [11, 18-20].*

2.4 Existing regulation ignores exposure synergies of pollutants

The [European Environment Agency's 2024 report](#) attributes 239,000 premature deaths in the EU to PM_{2.5}, 48,000 to NO₂, and 70,000 to ground-level ozone. Transportation noise adds another estimated 73,000 premature deaths and 49,000 cardiovascular disease cases annually ([EEA, Environmental Noise in Europe 2025 and 2026 corrigendum](#)).

These figures are calculated using current exposure levels and existing hazard ratios. They do not yet account for synergies due to cumulative exposures and the increased risk when people are exposed to multiple pollutants simultaneously. The evidence consistently indicates that cumulative burden models would yield higher estimates of attributable harm. This is the basis of Key Message 4.

In practice, the evidence in this section gives policymakers four established findings: a widespread exposure that EU law does not yet limit (Key Message 1), a quantified and large health burden (Key Message 2), health effects at concentrations below current limit values (Key Message 3), and combined exposures that compound the risk (Key Message 4). The options in Section 4 translate these findings into courses of action.

3 THE POLICY GAP What the AAQD does not do?

The [2022 revision of the AAQD and Directive \(EU\) 2024/2881](#) made meaningful progress but preserved the single-pollutant annual-mean architecture that has defined EU air quality law since the 1990s. Four gaps are directly relevant to the evidence presented above.

Gap	Current AAQD and DIRECTIVE (EU) 2024/2881 position	What exposome evidence shows
No UFP regulation	UFPs (<100 nm) are monitored at supersites under Art. 10, but no limit value, target value or exposure reduction obligation exists.	UFPs cause an estimated 419,000 new CVD cases per year in the EU. Mortality burden is comparable to regulated pollutants.
WHO EU alignment gap	PM _{2.5} EU 2030 target (10 µg/m ³) is twice higher than the WHO 2021 guideline (5 µg/m ³). No binding pathway to the WHO 5 µg/m ³ is embedded in law.	Health effects are documented at concentrations well below 10 µg/m ³ . The gap implies preventable disease and deaths.
Single-pollutant logic	Limits are set independently per pollutant. No mechanism exists to account for combined or cumulative exposure.	Combined exposures can produce non-linear, synergistic health effects. Cumulative burden models yield higher risk estimates than single-pollutant models.
Annual averaging	Compliance is measured by averaging annually. Short-term concentration peaks are only partly captured by daily/hourly limits but may also account for hospitalizations and mortality [21].	Acute cardiovascular events, preterm births, and neurodevelopmental harms are associated with short-term exposure spikes, not only annual average.

Why act now rather than wait for the 2030 review?

Article 3 of Directive (EU) 2024/2881 requires the Commission to review EU air quality standards by 31 December 2030 (and every 5 years thereafter), assessing the latest scientific evidence (including data from supersite monitoring of UFPs, black carbon and ammonia) and whether additional pollutants should be covered. The 2028 review by Member States for air quality roadmap is therefore the first legally scheduled opportunity to integrate emerging evidence on UFPs, cumulative exposure, and vulnerable populations into EU air quality law. Delaying action would postpone health gains and increase future disease burden and associated compliance direct and indirect costs by an estimated €6 billion per year against benefits of €42–121 billion (e.g. health care costs and lack of productivity) (Commission impact assessment, 2022). This timing is why Key Messages 1 and 3 focus on the 2028 review.

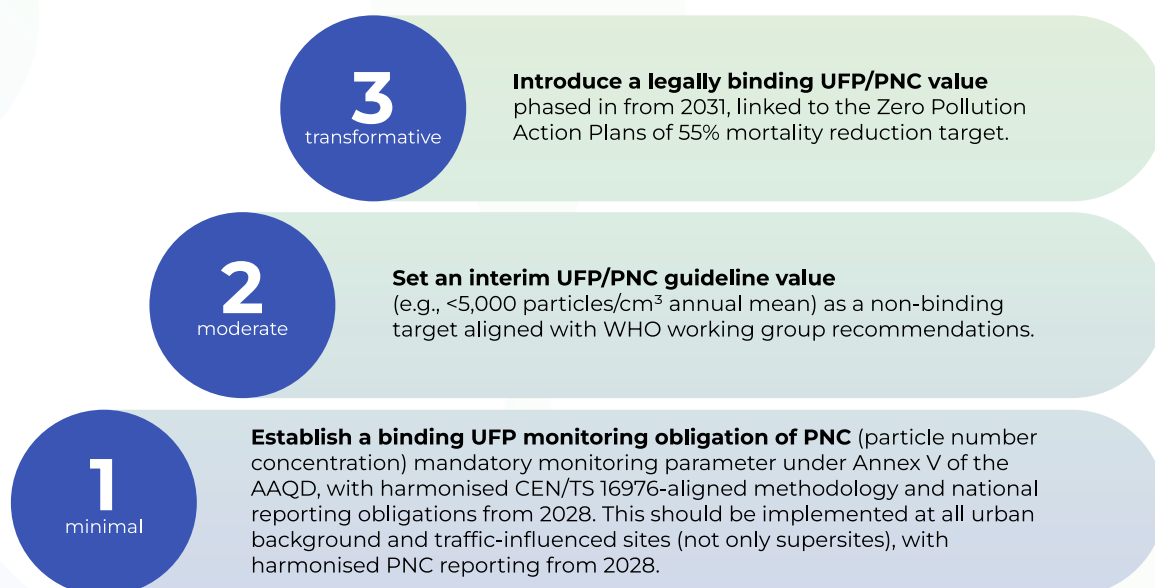
4 POLICY OPTIONS

Three Tiers of Action

The options below set out, in an advisory capacity, the evidence relevant to a range of possible measures. They are not mutually exclusive, and the choice of which to pursue rests with policymakers. Within each option, three tiers are presented in ascending order of ambition. Together they give effect to Key Message 5.

Option A: Extend limit value coverage to ultrafine particles

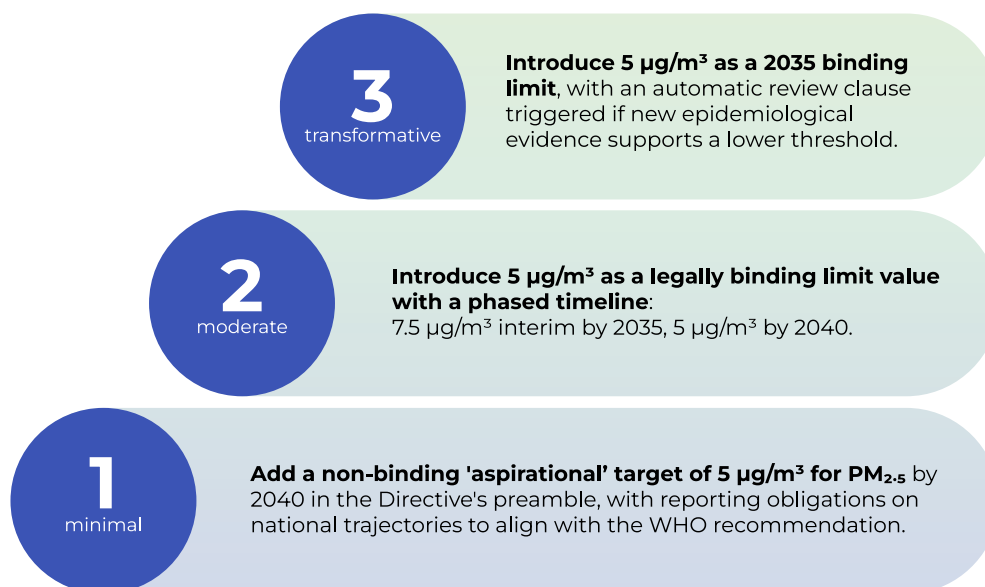
This is the most directly supported action. UFPs are already mandatorily monitored at EU supersites; their health burden is now measured at the EU scale; and the technical methodology for particle number concentration (PNC) measurement is mature. However, they remain unregulated.



Recommendations for Option A by tier. Tier 1: minimal impact to tier 3: transformative impact.

Option B: Embed pathway to WHO PM_{2.5} alignment

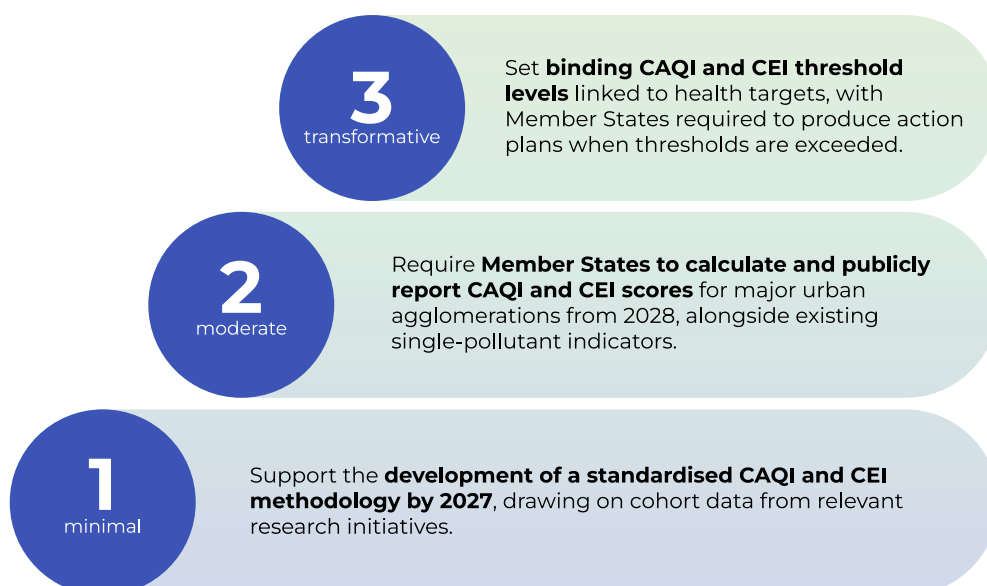
The 2030 EU limit of 10 µg/m³ is twice the WHO 2021 guideline. A clear legal pathway to 5 µg/m³ avoids endless deferral and gives Member States, industry and local authorities a planning horizon.



Recommendations for Option B by tier. Tier 1: minimal impact to tier 3: transformative impact.

Option C: Introduce Cumulative Exposure Index (CEI) as a reporting tool

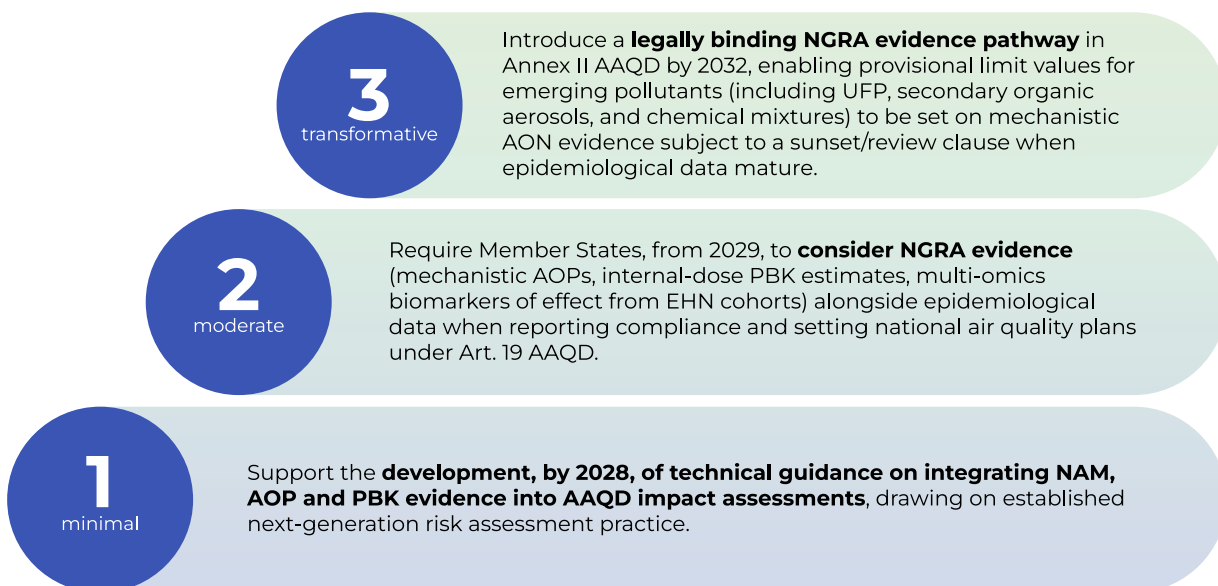
This option addresses the mixture gap. In addition to the already established Common Air Quality Index (CAQI), a Cumulative Exposure Index (CEI) would aggregate exposures across regulated and emerging pollutants (including UFP, NO₂, PM_{2.5}, ozone, transportation noise, and, where data allow, co-occurring chemical stressors, such as PFAS, plasticisers, heavy metals) using component-based mixture risk-assessment methodology aligned with the EU Chemical Mixtures Assessment Factor under REACH revision. The index would reflect cumulative health burden rather than single-pollutant exceedances, drawing on evidence from environmental research projects such as ENVESOME, EXPOSIM, MARKOPOLO, EXPANSE and HBM4EU.



Recommendations for Option C by tier. Tier 1: minimal impact to tier 3: transformative impact.

Option D: Recognise Next-Generation Risk Assessment (NGRA) evidence in AAQD limit-setting

This option addresses the regulatory-science gap. Where epidemiological exposure-response evidence remains heterogeneous (as it does for UFP, mixtures, and sensitive life-stage exposures) limit-setting requires a complementary mechanistic evidence base. NGRA integrates New Approach Methodologies (NAMs), Adverse Outcome Pathways and Networks (AOP/AON), physiologically based kinetic (PBK) modelling and multi-omics biomarkers into a defensible weight-of-evidence framework. This is the same regulatory-science direction already being pursued in the assessment of risks from chemicals, for example by the EURION cluster and the REACH revision, and its formal recognition under the AAQD would resolve the methodological asymmetry between EU chemicals and air-quality regulation.



Recommendations for Option D by tier. Tier 1: minimal impact to tier 3: transformative impact.

5 What policymakers can now

The Article 3 review is the legal milestone, but the political groundwork starts now. The near-term actions below translate the key messages into a concrete step for each institution:

- **For the European Commission (DG ENV):** commission an EEA technical report on UFP exposure–response functions and a feasibility assessment for a PNC limit value, to be delivered by Q2 2027, so that it is available when the supersite monitoring specifications are settled and well ahead of the Article 3 review.
- **For the European Environment Agency:** publish annual UFP supersite data and a pilot CEI for at least five major urban areas (2026–2027) to demonstrate operational feasibility.
- **For Member State environment ministries:** ensure full transposition of Directive (EU) 2024/2881 by December 2028, with national UFP monitoring infrastructure exceeding the minimum supersite requirements where feasible.
- **For the European Parliament (ENVI):** table an own-initiative report calling for a binding UFP limit value in 2030 in the Article 3 review, and use Parliament’s right under Article 225 TFEU to request a legislative proposal if the Commission does not act.
- **For health ministries and DG SANTE:** integrate UFP and cumulative-exposure indicators into the EU Cardiovascular Health Plan, Beating Cancer Plan and the comprehensive approach to mental health, linking air quality reform to the WHO 9 Global NCD targets and to the Sustainable Development Goal 3.4 (one-third reduction in NCD mortality by 2030).

6 Feasibility and Legal Basis

All the options are legally grounded in the existing AAQD framework and TFEU Article 192 (environmental policy, ordinary legislative procedure, qualified majority). None requires Treaty change. Early action on these provisions is also consistent with EU industrial competitiveness: aligning chemical, air and noise regulation under a coherent exposome-based framework (as advanced by the PARC Early Warning System and signalled by the REACH revision and the 8th Environment Action Programme) reduces regulatory uncertainty for industry while accelerating health gains.

Option	Legal basis	Lead actor	Key constraint/enabler
UFP limit value	Directive (EU) 2024/2881 Art. 3 (scope), Art. 7 (limit values), Art. 10 (monitoring), Annexes I & VII; TFEU Art. 192(1).	DG ENV with EEA technical lead	Requires standardised PNC monitoring network. EEA pilot programme feasible 2026-2027.
WHO PM_{2.5} alignment	AAQD Art. 7 (limit values) + Art. 3 (objectives)	DG ENV + Member States	Politically negotiated phase-in (2035 interim, 2040 final). Enabler: WHO 2021 evidence base; PARC mechanistic AOP/AON support; co-benefits with the European Health Data Space (EHDS) exposure-outcome linkage.
CEI	AAQD Art. 19 (air quality plans) + Art. 27 (information to the public); consistent with Zero Pollution Action Plan monitoring framework	EEA (methodology) + Member States (reporting)	Requires standardised mixture-RA methodology aligned with the EU Chemical Mixtures Assessment Factor under REACH revision; EHN cluster (EXPANSE, HBM4EU, ENVESOME, EXPOSIM, MARKOPOLO) can deliver the cohort evidence base. Enabler: Zero Pollution Action Plan reporting cycle.
NGRA evidence pathway	AAQD Annex II (assessment criteria) + Art. 4 (definitions); TFEU Art. 191(3) (precautionary principle and best scientific evidence)	DG ENV + DG RTD + EEA + PARC	Methodological alignment with EFSA and ECHA NGRA practice already established. Enabler: PARC, the EURION cluster, ENVESOME and the wider chemicals-policy direction; the EHN cluster delivers the multi-omics and AOP/AON evidence base directly.

7 Alignment with EU and global NCD frameworks

Air quality reform is not only an environmental policy; it is a non-communicable disease (NCD) prevention policy. Each option directly supports existing EU and global health commitments:

- **Zero Pollution Action Plan (2021):** 2030 target of reducing premature deaths from air pollution by 55% (vs 2005). UFP regulation closes the largest unmeasured contributor to this target.
- **European Beating Cancer Plan (2021):** recognises air pollution as a carcinogen. UFP limits would strengthen primary prevention.
- **EU Cardiovascular Health Plan (in preparation, 2026):** an EU-level cardiovascular framework is being scoped; UFP regulation is a logical component given the 419,000 attributable CVD cases/year.
- **WHO 9 Global NCD targets and SDG 3.4:** one-third reduction in premature NCD mortality by 2030. Air pollution is a key modifiable risk factor.
- **European Health Union and EU4Health 2021–2027:** explicit cross-sectoral mandate for environmental determinants of health.
- **8th Environment Action Programme (to 2030):** commits the EU to reduce significantly key environmental health risk factors including air, noise and chemical pollution.

8 About the ExpoHealthNet cluster and its future activities towards UFP regulation

The [ExpoHealthNet \(EHN\)](https://www.expohealthnet.eu) cluster unites seven cutting-edge research projects to investigate how environmental stressors contribute to non-communicable diseases (NCDs), including respiratory, cardiovascular, mental health, and immune-mediated conditions (summarized in Figure 2). The EHN cluster comprises 27 countries, 107 institutions, a total funding budget of 56.7 million EUR and spans a funding period of 60 months (started in 01/2025). By fostering collaboration and knowledge exchange, EHN aims to drive impactful research on the health risks of air pollution, noise, hazardous waste, and climate change. Project websites are at www.expohealthnet.eu.

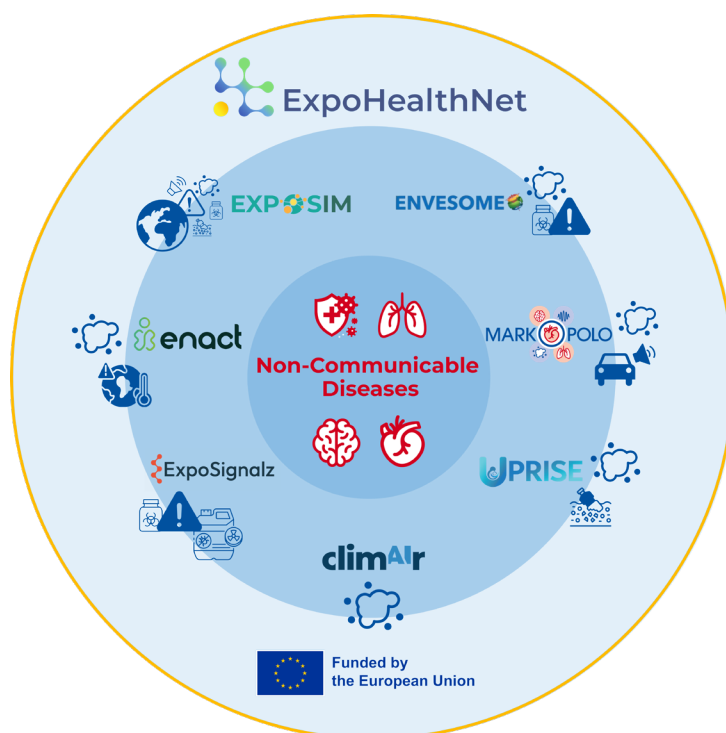


Figure 2. Expertise of consortia in ExpoHealthNet at a glance.

climAir [climAir](#): ClimAir explores how air pollution, climate change, global warming and combined environmental exposures, including fine and ultrafine particles, affect allergic rhinitis (AR) severity, symptom control and medication needs. It also examines pollution-modified immune responses to allergenic pollen using epigenetic, microbiota, proteomic and metabolomic approaches in AR patients, contributing to research on cumulative exposure, mixture risk evaluation and climate-sensitive respiratory health. Health outcome expertise: Primary focus: non-communicable respiratory diseases (AR); Secondary focus: air pollution and climate change determinants affecting AR.

enact [ENACT](#): Focus on integrated environmental exposures (air pollution, noise, temperature, greenness, light) using a multi-factor exposomic approach. Development of AI-driven risk models and decision-support systems combining environmental, clinical, and behavioural data. Implementation across five European pilots addressing cardiovascular, respiratory, dermatological, and ocular NCDs using wearable and environmental monitoring

data. Co-creation-based design with harmonised data, models, and KPIs across sites. Health outcome expertise: environmental-driven NCDs; and exposome-based risk prediction and preventive, personalized healthcare (adults and paediatric).

ENVESOME  **ENVESOME**: Focuses on emerging airborne pollutants (UFP, black carbon, aeroallergens, mineral dust), complex chemical mixtures (plasticisers, heavy metals, PFAS, PCBs, dioxins/furans) and co-occurring physical stressors (noise, light at night). It integrates multi-omics (genome-wide DNA methylation, microRNA from extracellular vesicles, transcriptomics, proteomics and untargeted metabolomics) with biomarkers of respiratory sensitisation, systemic inflammation, oxidative stress and cardiometabolic function, and with targeted and non-target chemical analysis of biological samples. ENVESOME translates this evidence into Adverse Outcome Networks (AONs), physiologically based kinetic (PBK) models and Next-Generation Risk Assessment (NGRA) deliverables intended to inform regulatory limit-setting under mechanistic uncertainty. Health outcome expertise: Most major forms of NCDs, immunotoxicity (IT), sleep disorders (SD), and mental health disorders (MHD).

ExpoSignalz  **EXPOSIGNALZ**: Focuses on the impact of chemical exposure, including persistent organic pollutant (PoPs), emerging pollutants as e-waste-related heavy metals, pharmaceuticals residues, pesticides. on brain from neurodevelopment to ageing. Several experimental approaches are used: In vitro models to study aggregation of amyloids, neuronal morphology, cell viability, neuronal network activity, markers. Cellular models in iPSC, neuronal activity, inflammatory markers, A β and P-Tau biomarkers associated with Alzheimer's disease (AD) and transcriptomic analyses. In vivo studies are performed behavioural in young and adult mice to assess behavioural alterations. Human cohort studies aim to identify exposome markers in blood, urine and hair using MS analyses. Blood biomarkers related to AD (A β and P-Tau181) are also investigated. Health outcome expertise: Primary focus: cognitive impairments and decline from mid-life to older age and dementia, including AD; Secondary focus: neuropsychiatric diseases (e.g. autism and ADHD).

EXP  **EXPOSIM**: Focus on environmental factors and effects on the immune system during pregnancy/early childhood and occupational exposures. Environmental factors studied are: air pollution (particles and gases), noise pollution, hazardous waste and chemicals, green/blue space access. Focus on human cohorts in which a large number of immune related variables will be studied with a focus on finding causal relationships between exposure and health effects. Modelling of UFP may be possible for the Danish EXPOSIM cohort. Health outcome expertise: Primary focus: Autoimmune diseases (e.g. arthritis, lupus; asthma). Secondary focus: Respiratory diseases (e.g. COPD) and cardiovascular diseases (e.g. CAD), functional immune system outcomes and vaccine efficacy.

MARKOPOLO  **MARKOPOLO**: Focus on traffic noise and/or air pollution with emphasis on UFPs and combined exposure effects. Mechanisms in brain, heart/vessel, lung: stress hormones, inflammation, oxidative stress, circadian clock, metabolic changes – multi omics (phospho/redox-proteomics, spatial epigenetics & DNA methylation, metabolomics, transcriptomics). Translation by interventional cohort studies (noise in obese versus lean subjects; noise and PM on metabolic syndrome and mitigation by healthy diet and exercise) and large Swiss and Danish national cohorts (>8 and >5 million people, linked to multiple exposures). Computational exposure-response approaches. Advanced bioinformatics. Social science approach on understanding knowledge transfer between science and policy.

Health outcome expertise: Primary focus CVD and death; Secondary focus neurodegeneration, respiratory disease, cancer.

UPRISE UPRISE: Focus on exposure to airborne Ultrafine Particles (UFPs) and Micro and Nano Plastics (MNPs) through advanced modelling and monitoring studies. Multi-omics: epigenomics and RNA-seq; Biochemical analysis of blood, urine, placenta tissue, and cord blood; Pregnant exposure devices and questionnaires, and Ages and Stages Questionnaires will be used for the newborn follow-up. Health outcome expertise: NCDs, foetal development, risk of adverse birth outcomes causal association of PM exposure during pregnancy, with small for gestational age (SGA), low birth weight (LBW), intrauterine growth restriction (IUGR), and prematurity or preterm birth (PTB).

9 Abbreviations

AAQD	Ambient Air Quality Directive (Directive (EU) 2024/2881)
AON	Adverse outcome network
AOP	Adverse outcome pathway
CAQI	Common Air Quality Index
CEI	Cumulative Exposure Index
CVD	Cardiovascular disease
DG ENV	European Commission, Directorate-General for Environment
DG SANTE	European Commission, Directorate-General for Health and Food Safety
ECHI	European Core Health Indicators
EEA	European Environment Agency
EHDS	European Health Data Space
EHN	ExpoHealthNet, the research cluster that produced this brief
ENVI	European Parliament Committee on the Environment, Public Health and Food Safety
GBD	Global Burden of Disease
NAM	New approach methodologies
NCDs	Non-communicable diseases
NGRA	Next generation risk assessment
NO ₂	Nitrogen dioxide
O ₃	Ozone
PBK	Physiologically based kinetic
PM	Particulate matter
PM _{2.5}	Fine particulate matter, 2.5 micrometres in diameter or less
PNC	Particle number concentration
TFEU	Treaty on the Functioning of the European Union
UFP	Ultrafine particle
WHO	World Health Organization

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