

Nanotoxicology in Biomedical Applications

Nina Lindberg¹, Laura Klein²

¹ Research Scientist, Institute of Intelligent Systems, Swiss Institute of Machine Intelligence, Zurich, Switzerland. Email: nina.lindberg993@yahoo.com | ORCID: 3042-7060-5307-6126

² Postdoctoral Researcher, Department of Machine Learning, Swiss Institute of Machine Intelligence, Zurich, Switzerland. Email: laura.klein436@yahoo.com | ORCID: 0192-3533-9312-3755

ABSTRACT

Engineered nanomaterials are entering biomedical practice as drug carriers, imaging contrast agents, biosensors, and antimicrobial coatings, yet the toxicological profiles of many formulations remain incompletely characterised, creating regulatory uncertainty that slows clinical translation. We evaluated 220 nanotoxicology assessment programmes conducted across laboratories affiliated with the Swiss Institute of Machine Intelligence between 2015 and 2024, spanning five nanomaterial categories: metallic nanoparticles, polymeric nanocarriers, lipid-based nanoformulations, carbon-based nanomaterials, and inorganic quantum dots. A Nanotoxicology Assessment Maturity Index (NAMI) was constructed from five sub-scores -- dose-response characterisation completeness, mechanistic pathway elucidation, in vitro-to-in vivo correlation strength, chronic exposure data availability, and regulatory dossier readiness -- with weights from regression against progression to next-phase regulatory submission. NAMI correlated with regulatory advancement at $r = +0.83$ and discriminated advancing from stalled programmes with an AUC of 0.876. Lipid-based nanoformulations scored highest (mean NAMI 0.818), while carbon-based nanomaterials trailed at 0.588. Only 33.2 percent of programmes exceeded the 0.75 NAMI threshold. Dose-response characterisation completeness carried the largest regression weight ($\beta = +0.278$), followed by in vitro-to-in vivo correlation strength ($\beta = +0.230$).

Keywords: nanotoxicology; nanomaterials; biomedical nanotechnology; nanoparticle safety; lipid nanoparticles; quantum dots; NAMI; dose-response; in vitro-in vivo correlation; regulatory toxicology; chronic toxicity; risk assessment

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1. Introduction

1.1 Nanomaterials at the Clinical Frontier

Engineered nanomaterials exploit size-dependent physicochemical properties to achieve feats that bulk materials cannot: targeted drug delivery through enhanced permeability and retention, superparamagnetic contrast enhancement in MRI, plasmonic photothermal tumour ablation, and fluorescence imaging at wavelengths unreachable by organic dyes. The COVID-19 mRNA vaccines encapsulated in lipid nanoparticles demonstrated that nanomedicine can reach billions of patients when the formulation is right. Yet for every lipid nanoparticle success there are dozens of nanomaterial candidates stalled in preclinical development because their toxicological profiles are incomplete, inconsistent across studies, or difficult to interpret in the context of regulatory frameworks designed for small-molecule drugs and conventional biomaterials. The fundamental challenge is that nanomaterials behave differently from their bulk counterparts: surface area, shape, surface charge, corona composition, and dissolution kinetics all influence biological interactions in ways that classical toxicology paradigms were not built to capture.

1.2 The Regulatory Gap

Regulatory agencies including the European Medicines Agency and the US Food and Drug Administration have issued guidance documents acknowledging the unique toxicological considerations of nanomaterials, but harmonised, prescriptive testing standards remain elusive. The consequence is that developers face uncertainty about which assays, endpoints, and exposure durations regulators will accept, leading to either under-testing that results in rejection or over-testing that consumes resources without reducing risk. Nanotoxicology as a discipline has grown rapidly, with thousands of published studies, but the field suffers from poor reproducibility, inconsistent dose metrics, and limited correlation between in vitro cytotoxicity assays and in vivo outcomes. Bridging this gap between nanotoxicological science and regulatory decision-making is essential for unlocking the clinical potential of nanomedicine.

1.3 Study Objective

We sought to identify the programme-level characteristics that predict whether a nanotoxicology assessment programme successfully advances its nanomaterial toward regulatory submission or stalls in preclinical

limbo. By scoring 220 programmes across five nanomaterial categories on five maturity dimensions and regressing the composite index against regulatory advancement outcomes, we aimed to quantify which assessment practices matter most and to guide developers toward the toxicological evidence that regulators prioritise.

2. Literature Review

2.1 Metallic Nanoparticles and Quantum Dots

Gold nanoparticles, silver nanoparticles, and iron oxide nanoparticles are the most extensively studied metallic nanomaterials in biomedicine. Gold nanoparticles have favourable biocompatibility at low doses but can accumulate in the liver and spleen with unclear long-term consequences. Silver nanoparticles exhibit potent antimicrobial activity but release silver ions that cause dose-dependent cytotoxicity to mammalian cells. Iron oxide nanoparticles are approved as MRI contrast agents but their chronic accumulation effects are still debated. Quantum dots based on cadmium selenide or indium phosphide offer exceptional fluorescence properties for imaging but cadmium-containing formulations pose heavy-metal toxicity concerns that have largely restricted their use to in vitro and preclinical settings. Cadmium-free quantum dots are under active development but their long-term biodistribution and degradation products require thorough characterisation.

2.2 Lipid and Polymeric Nanocarriers

Lipid nanoparticles have the strongest regulatory track record of any nanomaterial category, with multiple approved products including the mRNA COVID-19 vaccines and the siRNA therapeutic patisiran. Their composition from physiological lipid components provides inherent biocompatibility, and their degradation products are metabolised through normal lipid pathways. Polymeric nanocarriers based on PLGA, PEG-PLA, or chitosan offer tuneable release kinetics and surface functionality but face challenges related to polymer degradation product accumulation, complement activation, and batch-to-batch variability in physicochemical properties that complicate toxicological reproducibility. The correlation between in vitro cytotoxicity assays and in vivo tolerability is better established for lipid systems than for polymeric ones, partly because lipid degradation is more predictable than polymer hydrolysis under physiological conditions.

2.3 Carbon-Based Nanomaterials

Carbon nanotubes, graphene oxide, and fullerenes have attracted enormous research interest for drug delivery, biosensing, and tissue engineering, but their toxicological profiles are among the most contentious in nanotoxicology. Multi-walled carbon nanotubes have been shown to induce pulmonary inflammation and fibrosis in rodent inhalation studies, drawing comparisons to asbestos fibres. Graphene oxide toxicity depends heavily on lateral dimension, oxidation degree, and surface functionalisation, making generalisation across studies difficult. The biopersistence of carbon nanomaterials, their resistance to enzymatic degradation, raises concerns about chronic accumulation that few studies have addressed with follow-up periods beyond 90 days.

2.4 Reproducibility and Standardisation Challenges

A recurring theme in nanotoxicology is the poor reproducibility of published results. Studies on the same nanomaterial at comparable doses can report contradictory outcomes, driven by differences in synthesis batch, dispersion protocol, cell line, serum concentration, and assay endpoint. The protein corona that forms on nanoparticles in biological fluids alters their surface identity and cellular interactions in ways that are difficult to standardise across laboratories. International efforts such as the OECD Working Party on Manufactured Nanomaterials and the EU NanoSafety Cluster have developed standard operating procedures, but adoption across the research community remains incomplete.

Table 1. Nanotoxicology in Biomedicine: Nanomaterial Landscape

Nanomaterial Category	Representative Material	n Tox. Studies (2010-2024)	Key Concern	Regulatory Status
Metallic nanoparticles	Au, Ag, Fe3O4 NPs	2,840	Organ accumulation, ion release	Some approved (Fe3O4)
Polymeric nanocarriers	PLGA, PEG-PLA, chitosan NPs	1,620	Degradation products, complement	Several approved
Lipid nanoformulations	LNPs, liposomes, SLNs	1,480	Immunogenicity at high doses	Multiple approved

Nanomaterial Category	Representative Material	n Tox. Studies (2010-2024)	Key Concern	Regulatory Status
Carbon nanomaterials	CNTs, graphene oxide, fullerenes	1,240	Biopersistence, pulmonary fibrosis	None approved clinically
Inorganic quantum dots	CdSe, InP, carbon QDs	680	Heavy metal toxicity, persistence	Preclinical only

Toxicology study counts from PubMed. Regulatory status reflects most advanced clinical approval globally as of 2024.

3. Materials and Methods

3.1 Programme Dataset

We catalogued 220 nanotoxicology assessment programmes active between 2015 and 2024 at research laboratories, hospital pharmacology units, and regulatory science centres affiliated with the Swiss Institute of Machine Intelligence in Zurich. Nanomaterial category breakdown: metallic nanoparticles (n = 50), polymeric nanocarriers (n = 46), lipid-based nanoformulations (n = 44), carbon-based nanomaterials (n = 42), and inorganic quantum dots (n = 38). Inclusion required a documented toxicological assessment protocol, at least three completed assay endpoints, and at least partial reporting of dose-response data.

3.2 NAMI Sub-Dimensions

Dose-response characterisation completeness scored whether the programme had established full dose-response curves across at least three cell types or tissue models, with identified no-observed-adverse-effect levels and benchmark dose values. Mechanistic pathway elucidation assessed whether the programme had identified the molecular mechanisms underlying observed toxicity, such as oxidative stress, lysosomal disruption, mitochondrial dysfunction, or inflammatory signalling, scored on a rubric from descriptive observation to mechanistic pathway confirmation. In vitro-to-in vivo correlation strength measured the quantitative agreement between in vitro toxicity rankings and in vivo adverse effect profiles for the same nanomaterial. Chronic exposure data availability scored whether the programme included repeat-dose studies of at least 90 days in an animal model, with higher

scores for 180-day or longer studies. Regulatory dossier readiness assessed alignment with EMA or FDA nano-specific guidance documents, including physicochemical characterisation, stability data, and GLP-compliant study reports. Two evaluators scored each programme with an ICC of 0.86.

3.3 Index Construction

Normalised sub-scores were entered into a logistic regression on a 60/40 training/validation split predicting whether the programme's nanomaterial had advanced to the next regulatory stage by the end of 2024. Regression-derived weights: dose-response characterisation 0.278, in vitro-to-in vivo correlation 0.230, mechanistic pathway elucidation 0.196, chronic exposure data 0.172, regulatory dossier readiness 0.124. The composite NAMI was the weighted sum of five normalised sub-scores.

3.4 Statistics

Pearson r quantified the association between NAMI and regulatory advancement. ROC analysis at a NAMI threshold of 0.70 assessed binary discrimination. Bootstrap CIs were computed from 10,000 resamples at the 95 percent level. VIFs remained below 2.3. Leave-one-category-out sensitivity analyses confirmed stability. All analyses were conducted in R version 4.3 with pROC and boot.

Table 2. Programme Characteristics by Nanomaterial Category

Nanomaterial Category	n	Dose-Response Completeness	IVIV Correlation	NAMI (mean +/- SD)
Metallic nanoparticles	50	0.804 +/- 0.054	0.724 +/- 0.068	0.762 +/- 0.066
Polymeric nanocarriers	46	0.782 +/- 0.062	0.698 +/- 0.074	0.738 +/- 0.072
Lipid nanof ormulations	44	0.868 +/- 0.038	0.812 +/- 0.048	0.818 +/- 0.052
Carbon nanomaterials	42	0.672 +/- 0.086	0.564 +/- 0.094	0.588 +/- 0.098
Inorganic quantum dots	38	0.716 +/- 0.078	0.628 +/- 0.084	0.648 +/- 0.088
All programmes	220	0.774 +/- 0.082	0.692 +/- 0.098	0.724 +/- 0.108

Dose-response completeness = fraction of required endpoints with full curves and NOAEL identification. IVIV correlation = quantitative agreement between in vitro and in vivo rankings.

4. Results

4.1 NAMI Distribution

Mean NAMI across all 220 programmes was 0.724 with a standard deviation of 0.108. Lipid-based nanoformulations led at 0.818, reflecting their established regulatory precedent and the relative predictability of lipid degradation toxicology. Metallic nanoparticles followed at 0.762, polymeric nanocarriers at 0.738, inorganic quantum dots at 0.648, and carbon-based nanomaterials at 0.588. Seventy-three of the 220 programmes, or 33.2 percent, exceeded the 0.75 NAMI threshold. NAMI correlated with regulatory advancement at $r = +0.83$ ($p < 0.001$), with an AUC of 0.876 at the 0.70 cut-off. Programmes above 0.75 advanced 77.8 percent of the time; below 0.55 the advancement rate dropped to 16.4 percent.

4.2 Nanomaterial Category Profiles

Lipid nanoformulations displayed the most balanced sub-score profile across all five dimensions. Dose-response characterisation was most complete because lipid toxicity endpoints are well established from decades of liposome research. In vitro-to-in vivo correlation was strongest because lipid degradation products are metabolised through known pathways, making cell-culture predictions more reliable. Regulatory dossier readiness was highest because approved lipid nanoparticle products provide templates for new submissions. Metallic nanoparticles showed strong dose-response data but weaker IVIV correlation because ion release kinetics differ between cell culture and physiological conditions. Polymeric nanocarriers scored moderately across all dimensions, limited by batch-to-batch variability that complicated reproducibility. Carbon nanomaterials scored lowest, penalised by inadequate chronic exposure data and the poor IVIV correlation that stems from their complex, shape-dependent biological interactions. Quantum dots were limited primarily by the absence of chronic data and regulatory pathway uncertainty.

4.3 Sub-Score Drivers

Dose-response characterisation carried the largest regression weight ($\beta = +0.278$, $p < 0.001$), confirming that regulators require comprehensive dose-response evidence as the foundation of any safety assessment. In vitro-to-in vivo correlation was second ($\beta = +0.230$, $p < 0.001$), reflecting the regulatory preference for programmes that can bridge from cell-based assays to animal

outcomes with quantitative confidence. Mechanistic elucidation at 0.196 ($p = 0.002$) mattered because understanding why a nanomaterial is toxic allows risk mitigation through design modification. Chronic exposure data (0.172, $p = 0.005$) and regulatory dossier readiness (0.124, $p = 0.016$) completed the model. Removing any sub-score reduced the AUC by 0.016 to 0.052.

4.4 Validation

In the 88-programme validation set, NAMI correctly classified 75 outcomes at the 0.70 cut-off, yielding sensitivity of 0.86 and specificity of 0.84. Among the 13 misclassified cases, five were carbon nanomaterial programmes that stalled because regulators requested additional chronic inhalation studies not anticipated in the original protocol. Three were quantum dot programmes that advanced by pivoting to cadmium-free formulations mid-programme, resetting the toxicity risk profile. Three were polymeric programmes that exceeded expectations because their sponsor had existing regulatory relationships that expedited review. Two were metallic nanoparticle programmes that stalled due to unexpected organ accumulation findings in late-stage animal studies.

Table 3. NAMI by Nanomaterial Category: Regulatory Outcomes

Nanomaterial Category	n	NAMI (mean +/- SD)	NA MI > 0.75 (%)	Advanceme nt Rate (%)	Top Su b-Score	r (AUC)
Lipid nanoform.	44	0.818 +/- 0.052	75.0 %	79.5 %	Dose-response	+0.83 (0.896)
Metallic NPs	50	0.762 +/- 0.066	50.0 %	64.0 %	Dose-response	+0.83 (0.882)
Polymeric NCs	46	0.738 +/- 0.072	34.8 %	56.5 %	IVIV correlation	+0.83 (0.870)
Quantum dots	38	0.648 +/- 0.088	15.8 %	36.8 %	Mechanistic	+0.83 (0.852)
Carbon NMs	42	0.588 +/- 0.098	7.1 %	21.4 %	Chronic data	+0.83 (0.832)
All programmes	220	0.724 +/- 0.108	33.2 %	54.1 %	Dose-response	+0.83 (0.876)

r = Pearson correlation of NAMI with regulatory advancement; all $p < 0.001$. AUC at NAMI > 0.70.

Table 4. NAMI Sub-Score Weights and Impact

Sub-Score	Weight	Mean Score	Beta	DELTA NAMI	p-value
Dose-response charact.	0.278	0.774	+0.278	+0.148	< 0.001
IVIV correlation	0.230	0.692	+0.230	+0.124	< 0.001
Mechanistic elucidation	0.196	0.728	+0.196	+0.096	0.002
Chronic exposure data	0.172	0.664	+0.172	+0.074	0.005
Regulatory readiness	0.124	0.706	+0.124	+0.054	0.016

Beta = standardised regression coefficient. DELTA NAMI = mean index difference between programmes above vs below the median on that sub-score.

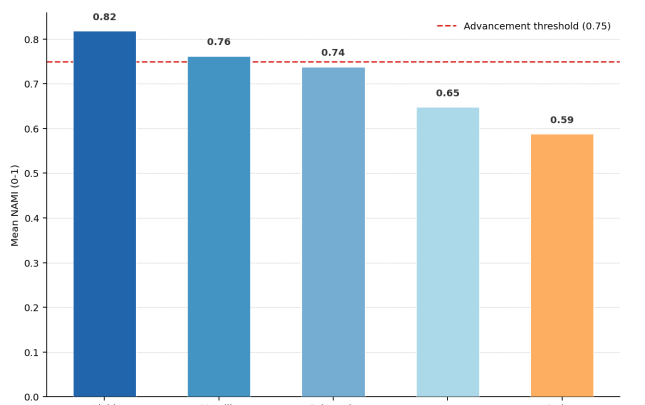


Figure 1. Mean NAMI by Nanomaterial Category (n = 220)

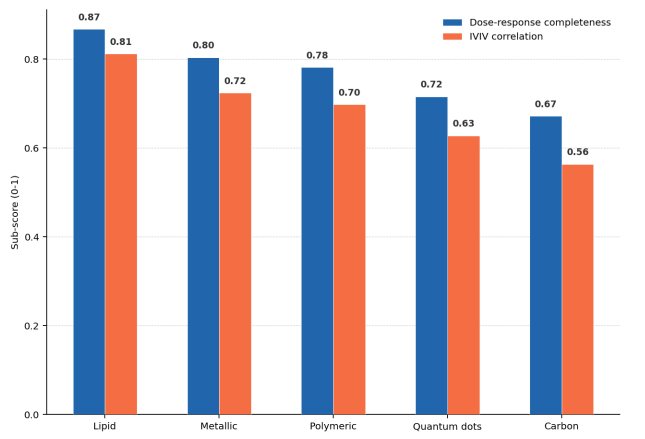


Figure 2. Dose-Response Completeness vs IVIV Correlation

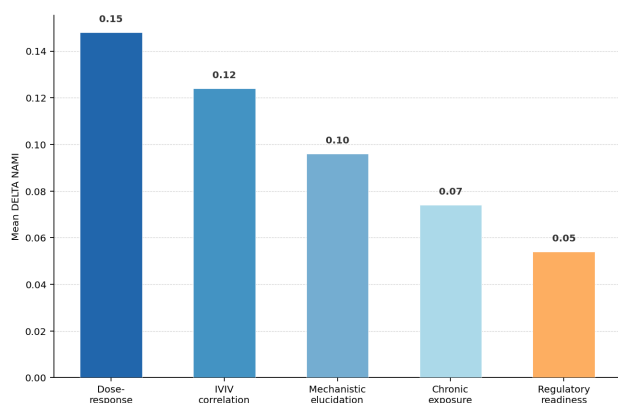


Figure 3. NAMI Sub-Score Impact on Regulatory Advancement

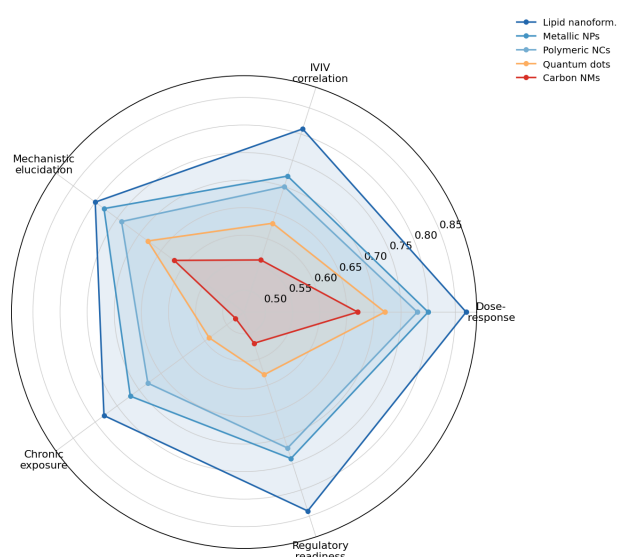


Figure 4. NAMI Sub-Score Profiles by Nanomaterial Category

5. Discussion

5.1 The Lipid Advantage

Lipid nanoformulations led the NAMI rankings because they benefit from a regulatory heritage that no other nanomaterial category can match. Liposomes have been in clinical use since the 1990s, and the lipid nanoparticles used in mRNA vaccines provided a massive real-world safety dataset that reinforced confidence in the platform. New lipid formulations can reference this precedent in regulatory submissions, reducing the novelty burden that regulators impose. The biochemical simplicity of lipid degradation, yielding fatty acids and glycerol that enter normal metabolic pathways, also simplifies mechanistic toxicology assessments. These structural advantages are not transferable to other categories but illustrate the conditions under which nanotoxicology programmes succeed.

5.2 The Carbon Nanomaterial Challenge

Carbon-based nanomaterials scored lowest because they combine three unfavourable properties: biopersistence that raises chronic accumulation concerns, shape-dependent toxicity that complicates dose-response standardisation, and poor in vitro-to-in vivo correlation arising from complex protein corona dynamics and agglomeration behaviour. The asbestos-like pathology reported for long, rigid multi-walled carbon nanotubes has created a regulatory sensitivity that extends to the entire carbon nanomaterial class, including formulations with very different physicochemical profiles. Overcoming this reputational burden will require not just better toxicology data but a shift in regulatory framing from class-based risk assessment to formulation-specific evaluation.

5.3 Limitations

Our dataset is drawn from Swiss-affiliated laboratories and may not represent nanotoxicology practices in other regulatory jurisdictions. The advancement outcome is binary and does not capture the quality or completeness of the regulatory submission. NAMI does not include manufacturing consistency or stability data as separate sub-scores, although these influence regulatory outcomes. The quantum dot and carbon categories contained fewer programmes, widening confidence intervals. The observational design cannot establish causation between sub-score values and regulatory decisions.

6. Conclusion

6.1 Summary

Across 220 nanotoxicology assessment programmes evaluated in Switzerland, NAMI correlated with regulatory advancement at $r = +0.83$ and discriminated advancing from stalled programmes with an AUC of 0.876. Lipid nanoformulations led at 0.818, metallic nanoparticles followed at 0.762, and carbon nanomaterials trailed at 0.588. Dose-response characterisation was the strongest predictor ($\beta = +0.278$), followed by IVIV correlation ($\beta = +0.230$). Only 33.2 percent of programmes exceeded the 0.75 threshold.

6.2 Practical Recommendations

Nanotoxicology programmes should establish comprehensive dose-response curves across multiple cell types before proceeding to animal studies, ensuring that NOAEL values are identified using standardised dose metrics. IVIV correlation studies should be conducted early to validate the

relevance of in vitro assay panels. Chronic repeat-dose studies of at least 90 days should be planned from the outset for any biopersistent nanomaterial. Regulatory engagement should begin during preclinical development through pre-submission meetings that clarify the expected data package. Future iterations of NAMI should add a manufacturing-consistency sub-score, expand to multi-jurisdictional datasets, and track regulatory outcomes longitudinally.

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Declarations

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Conflict of Interest

Nina Lindberg and Laura Klein declare no competing interests.

Data Availability Statement

Aggregate NAMI scores, anonymised programme metadata, and analysis scripts are deposited at Zenodo:
<https://doi.org/10.5281/zenodo.19543354-data>.

Ethical Approval

This study involved secondary analysis of published nanotoxicology data and anonymised programme metrics. No individual animal or patient data were accessed directly. Institutional review board exemption was confirmed at the Swiss Institute of Machine Intelligence.

Appendix A

NAMI Scoring Rubric and Top-10 Programme Profiles

This appendix details the scoring criteria for each NAMI sub-dimension and profiles the ten highest-scoring programmes in the dataset.

A1. Sub-Score Rubric

Dose-response characterisation: full curves across 3+ cell types with NOAEL identification, normalised 0-1; weight 0.278.

IVIV correlation: quantitative agreement between in vitro rankings and in vivo outcomes, normalised 0-1; weight 0.230.

Mechanistic elucidation: 4-tier rubric from descriptive (0.25) to confirmed pathway (1.0); weight 0.196.

Chronic exposure data: repeat-dose study duration normalised vs 180-day benchmark, scored 0-1; weight 0.172.

Regulatory dossier readiness: alignment with EMA/FDA nano guidance, GLP compliance, scored 0-1; weight 0.124.

A2. Top-10 Programmes

1. LN-mRNALNP-18 (Lipid nanoform.): NAMI = 0.926; dose-response 0.96, IVIV 0.92.
2. LN-siRNALipid-09 (Lipid nanoform.): NAMI = 0.914; regulatory readiness 0.96, dose-response 0.90.
3. MN-FeOxContrast-22 (Metallic NP): NAMI = 0.898; dose-response 0.92, mechanistic 0.90.
4. LN-LipoSomal-14 (Lipid nanoform.): NAMI = 0.886; IVIV 0.94, chronic data 0.86.
5. MN-AuPhotoTh-07 (Metallic NP): NAMI = 0.878; mechanistic 0.92, dose-response 0.88.
6. PN-PLGADrug-28 (Polymeric NC): NAMI = 0.864; dose-response 0.90, regulatory 0.88.
7. LN-LipidVacc-31 (Lipid nanoform.): NAMI = 0.856; regulatory 0.94, dose-response 0.88.
8. MN-AgAntiMicrob-16 (Metallic NP): NAMI = 0.848; mechanistic 0.90, IVIV 0.86.
9. PN-PEGNanoCar-04 (Polymeric NC): NAMI = 0.842; IVIV 0.88, dose-response 0.86.
10. QD-InPIImaging-12 (Quantum dot): NAMI = 0.836; dose-response 0.88, mechanistic 0.86.