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1 **Evaluating environmental risk assessment models for**
2 **nanomaterials according to requirements along the product**
3 **innovation Stage-Gate process**

4

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44 **Abstract**

45 Nanomaterial risk governance requires models to estimate the material flow, fate and transport
46 as well as uptake/bioavailability, hazard and risk in the environment. This study assesses the
47 fit of such available models to different stages during the innovation of nano-enabled products.
48 Through stakeholder consultations, criteria were identified for each innovation stage from idea
49 conception to market launch and monitoring. In total, 38 models were scored against 41
50 criteria concerning model features, applicability, resource demands and outcome parameters.
51 A scoring scheme was developed to determine how the models fit the criteria of each
52 innovation stage. For each model, the individual criteria scores were added, yielding an overall
53 fit score to each innovation stage. Three criteria were critical to stakeholders and incorporated
54 as multipliers in the scoring scheme; the required time/costs and level of expertise needed to
55 use the model, and for risk assessment models only, the option to compare PEC and PNEC.
56 Regulatory compliance was also identified as critical, but could not be incorporated, as a
57 nanomaterial risk assessment framework has yet to be developed and adopted by legislators.
58 In conclusion, the scoring approach underlined similar scoring profiles across stages within
59 model categories. As most models are research tools designed for use by experts, their score
60 generally increased for later stages where most resources and expertise is committed. In
61 contrast, stakeholders need relatively simple models to identify potential hazards and risk
62 management measures at early product development stages to ensure safe use of
63 nanomaterials without costs and resource needs hindering innovation.

64 **Introduction**

65 Advances in nanotechnology over the past decade have enabled the production and use of
66 engineered nanomaterials for different products and applications, representing an estimated
67 global annual market value of \$1 trillion.¹ The number of nano-enabled consumer products
68 available to European consumers has increased noticeably over this time covering a variety of
69 product categories from sporting goods to personal care and cleaning products.² The added
70 benefits of nanomaterials are often ascribed to their unique characteristics. By engineering key
71 features, such as coating, size or shape, it is possible to change properties, such as reactivity
72 and dispersion stability to support specific applications relevant to use in various products.³
73 However, the potential for such highly engineered nanomaterial properties to cause toxicity in
74 organisms following deliberate or accidental release to the environment has been a cause for
75 public and political concern. This has resulted in scientific and regulatory community calls for
76 timely risk assessment to identify and manage any potential adverse effects to human health
77 and the environment from engineered nanomaterials.

78
79 Currently, the environmental risk assessment of nanomaterials is based on procedures
80 originally conceived for the risk assessment of conventional chemicals,⁴ although the field is
81 developing. Approaches used for conventional chemicals consist of four main steps: hazard
82 identification, hazard characterisation, exposure assessment and risk quantification. For
83 nanomaterials, each of these steps presents challenges. The hazard identification is often
84 based on inherent physical and chemical properties, which differ for nanomaterials compared
85 to conventional chemicals.⁵ In the hazard assessment, establishing concentration-response
86 relationships for nanomaterials is more challenging because particle-specific processes such
87 as agglomeration and sedimentation often will cause exposure concentrations to fluctuate
88 during incubation.⁶ The exposure assessment is also challenged by particle-specific processes
89 such as homo- and heteroagglomeration, dissolution and reactivity, as well as the scarcity of
90 available data on nanomaterial use and production volumes and also issues with reliable
91 detection methods for model validation.⁷ As the final risk characterization phase compiles

92 information from all the previous steps, the limitations of each step towards the final
93 assessment add to the overall uncertainty of the final calculated risk quotient.⁵ The challenges
94 in conducting nanomaterial environmental risk assessment using traditional paradigms have
95 led to the development of alternative nano-specific modelling and decision support tools.
96 Examples include the “Precautionary Matrix for Synthetic Nanomaterials”⁸ and the LICARA
97 nanoSCAN.⁹ Furthermore, modelling approaches and tools originally developed for chemicals,
98 such as the species sensitivity distribution (SSD) and multimedia environmental fate models,
99 have been refined in the attempt to accommodate certain nanomaterial-specific properties and
100 behaviours in the environment, such as agglomeration and dissolution.^{10–14}

101
102 Several reviews of decision support tools or environmental assessment models available for
103 nanomaterials are published.^{15–24} In 2012, Brouwer¹⁶ discussed similarities and differences
104 between six control banding approaches proposed for nanomaterials, Grieger et al.¹⁵
105 evaluated eight alternative tools proposed for environmental risk assessment of nanomaterials
106 against ten criteria cited as important by various sources, including transparency, precaution
107 and life cycle perspective, and Hristozov et al.¹⁸ discussed the value of tools for risk
108 assessment and management of nanomaterials considering limitations and uncertainties in
109 key areas such as data availability. Later in 2016, Hristozov et al.¹⁷ extended their analysis to
110 48 tools, assessing potential utility for different aspects of risk assessment against 15
111 published stakeholder needs including nano-specific requirements, life cycle approach, pre-
112 assessment phase, and exposure-driven approach. No single tool was found to fully meet the
113 criteria, leading the authors to call for the development of a new tool that integrates data and
114 current models to support nanomaterial risk assessment and management. This conclusion
115 was broadly supported by Arvidsson et al.,¹⁹ following a review of 20 risk assessment
116 screening methods. Also in 2016, Baalousha et al.²¹ focused on the state-of-the-art of models
117 assessing nanomaterial fate and transport as well as uptake and accumulation in biota and
118 found that available models require calibration and validation using available data, rather than
119 extension to higher complexity and inclusion of further transformation processes. In line with

120 this, Nowack²³ evaluated environmental exposure models within a regulatory context in 2017.
121 The review concluded that some of the available fate models for nanomaterials are built on
122 concepts accepted by regulators for conventional chemicals, increasing the likelihood that
123 such nano-models will be accepted. It was found that a critical issue for all models is the
124 missing validation of predicted environmental concentrations by analytical measurements;
125 however, validation on a conceptual level was found to be possible.

126
127 Romero-Franco et al.²⁰ in 2017 evaluated the applicability of 18 existing models for assessing
128 the potential environmental and health impacts of nanomaterials based on six decision
129 scenarios, describing common situations of different stakeholders from manufacturers to
130 regulatory bodies who need to make decisions in matters concerning environmental health
131 and safety of nanomaterials. For all decision scenarios, at least one existing tool was identified
132 as capable of partly meeting the needs. Also with a focus on stakeholders, Malsch et al.
133 2017²⁵ presented a mental modelling methodology for comparing stakeholder views and
134 objectives in the context of developing a decision support system. A case study was
135 conducted among prospective users of the SUNDS decision support tool, mainly from industry
136 and regulators, which showed a greater interest in risk assessment decision support than in
137 sustainability assessment.

138
139 Some of the most recent reviews of nanomaterial environmental risk assessment methods is
140 that of Trump et al.²⁶ and Oomen et al.²² from 2018. Trump et al. 2018 reviewed the
141 nanomaterial tool development over time, and found that tools based on metrics of risk
142 (hazard and exposure assessment) have been the most common over the last 14 years,
143 control banding became more popular during the period of 2008-2012, whereas LCA and
144 decision analytical tools emerged most recently. The authors state that “no method dominates
145 in applicability and use over the others, within all context. Instead time, resource availability,
146 along with perceived stakeholder need, should guide which tool(s) should be used in a given
147 context”.²⁶ Oomen et al.²² considered 14 models or tools for prioritisation, ranking or assessing

148 nanomaterial safety, according to their fit to OECD defined criteria for regulatory relevance and
149 reliability. All except one tool were found to lack criteria enabling actual decision-making and
150 the authors suggest the development of an international pragmatic decision framework that is
151 only partially scientifically based. The scope is decision-making in regulatory contexts and in
152 the product development chain, and although conclusions briefly touch upon applicability of
153 the tools in the innovation chain, a complete matching of tools and Stage-Gates was not
154 conducted. An innovation chain Stage-Gate model, such as that presented by Cooper in
155 1990²⁷, is a structured approach for bringing a product idea to market launch as effectively as
156 possible while driving down the risk of spending resources on developing products, that will
157 never make it to market launch. Since its initial publication, the Stage-Gate model has become
158 an industrial standard for managing new product innovation processes.²⁸ In the Stage-Gate
159 approach, the overall innovation process is divided into discrete work stages, each ending in a
160 decision point (gate), where the process is reviewed against pre-defined decision criteria and a
161 decision is made on whether to terminate, continue, hold or recycle the product innovation
162 process (Figure 1). Usually the amount of resources committed increases along the stages,
163 and the quality of the information generated also becomes higher. As a result, the risk of
164 making incorrect decisions on the development of a product after having spent a great amount
165 of resources is lowered, as decisions can be made with increased certainty.²⁷

166
167 To our knowledge, none of the numerous reviews published have assessed nanomaterial
168 environmental assessment models against stakeholder needs for different applications during
169 specific stages of the product innovation chain, although a case-study focusing on graphene,
170 provides an overview of actions and actors during different stages of innovation that may help
171 achieve safe development of products including this nanomaterial.²⁹ In this study, we apply
172 such coupling of modelling tools to the Stage-Gate concept to enable the identification of tools
173 or approaches best suited at specific stages of innovation. At the different stages,
174 stakeholders need different model estimates, features and output for decision-making, and
175 they have varying resources allocated for risk assessment and safety-related work. Therefore

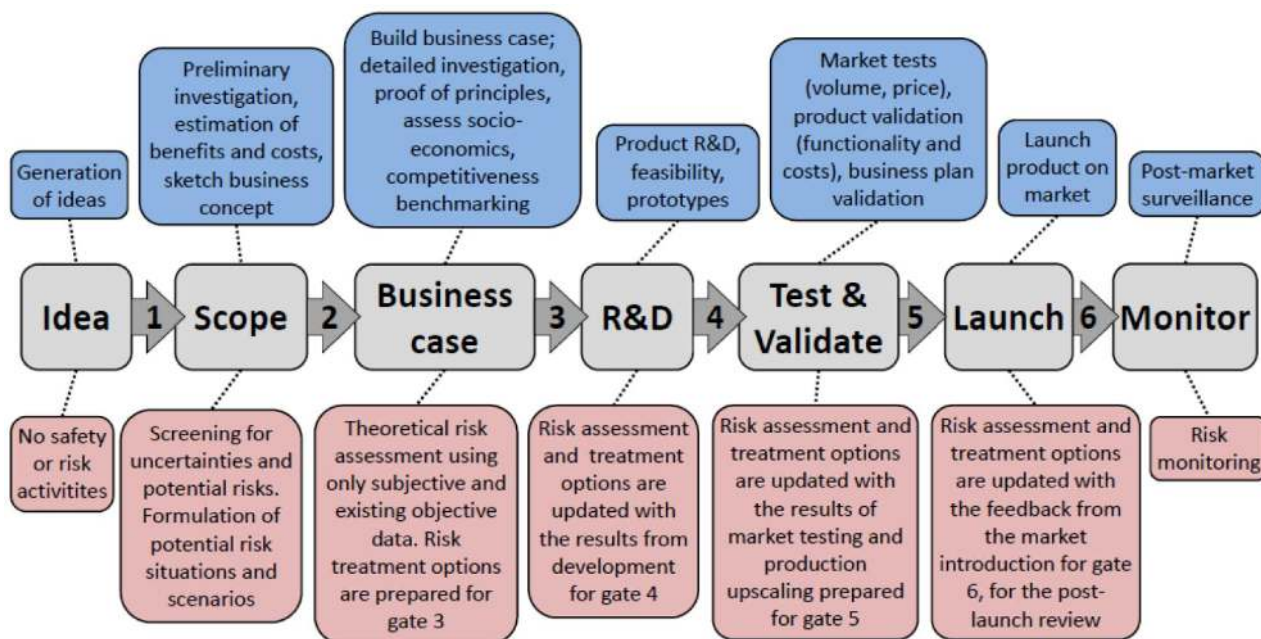
176 assessing how currently available models or tools match the needs of individual stages, allows
177 structured and effective use of the available tools to ultimately ensure safe use and
178 development of nanomaterials and nano-enabled products, without hampering innovation or
179 financial growth. Furthermore, the present study, conducted within the H2020 project
180 caLIBRAte, provides a semi-quantitative assessment, whereas most published reviews are
181 qualitative or narrative. We focus on selected environmental risk assessment models and
182 evaluate these according to requirements in the Stage-Gate process using input obtained
183 through a stakeholder consultation exercise. In total, 38 models/tools focused on the
184 assessment of nanomaterial flow, fate and transport, hazard, uptake/bioavailability or risk in
185 the environment, were assessed against 41 criteria. Feedback from 18 stakeholders assisted
186 the design of a scoring scheme to comparatively assess the model suitability to stakeholder
187 requirements at different stages of the innovation chain. The scoring scheme considers both
188 the fit against the defined criteria and weights model fit to stakeholder needs according to the
189 identified criteria.

190 Methods

191 Overall concept for model assessment

192 Published models or tools proposed for the assessment of nanomaterial flow, exposure,
193 hazard, uptake/bioavailability and risk in the environment were assessed against requirements
194 at different stages in product conception, development and application for nano-enabled
195 products. We used the Stage-Gate concept^{27,28} as an approach to track the suitability of
196 different models at different stages of innovation during potential product development. From
197 the EU FP7 project "Nanoreg II", descriptions of the safety-related activities in the various
198 stages have been obtained. An overview of the product innovation and safety activities in each
199 stage is provided in Figure 1.

200



201
202 **Figure 1.** Overview of product innovation (blue) and safety-related (red) activities reported by the EU
203 FP7 project "Nanoreg II" at the different stages of the product innovation process (grey) presented by
204 Cooper (1990)²⁷ and Edgett (2015)²⁸.

205
206 Within the chain, the level of information both needed for and required from models for
207 environmental risk assessment increases at each stage. In early stages, with little information
208 available about the materials or products in question, risk evaluation tools that can operate

209 with limited data may fit the needs of decision-makers better than at later stages, where
210 models with more extensive and specific data needs may be better suited. Hence, different
211 models may be required by users at different stages, with no single tool likely to be appropriate
212 for all potential needs within the chain. Identification of the tools best fitted to each stage can
213 facilitate optimal use of resources to enable efficient risk assessment.

214

215 **Identification of stakeholder needs along nanomaterial innovation**

216 To identify different stakeholders' needs from nanomaterial environmental assessment
217 models, a generic questionnaire was distributed to a selection of stakeholders to engender a
218 diversity of structured feedback. The questionnaire was prepared by listing potential
219 criteria/requirements for nanomaterial environmental assessment models based on previous
220 work and existing narrative literature on tool fit to stakeholder needs such as Hristozov et al.,
221 2016.¹⁷ The questionnaire contains two parts identifying requirements in two areas:

- 222 1. General model features, relevant to all model types, concerning applicability such as
223 required user resources and model features.
- 224 2. Model output parameters and features affecting the output of exposure, hazard and
225 risk assessment models, respectively.

226

227 The criteria for model output parameters were categorized as relating to aspects of material
228 flow, fate and transport, hazard, uptake/bioavailability or risk, recognizing though, that some of
229 the risk assessment models include sub-model(s) relating to one or more of the other
230 categories. As the purpose of the interviews was to identify what stakeholders need from
231 nanomaterial environmental assessment models during decision-making processes, the
232 criteria focus on model *outcome* parameters/information, although these outcomes are
233 obviously governed by input parameter availability and quality.

234

235 The questionnaire lists criteria (vertically) against product innovation stages (horizontally), thus
236 forming a table that stakeholders were each asked to complete. This allowed stakeholders to

237 provide feedback on their needs and requirements for each of the criteria at the individual
238 stages in Figure 1. If key criteria were found missing, the stakeholder could add these. For
239 each criterion, the response options used restricted selection, defined depending on the
240 question asked, including; yes/no, pick lists, tick off lists, and the rating of a criterions'
241 importance from 0 (not important) to 5 (essential), rather than free text options. Stakeholders
242 were encouraged to provide comments on these default response options to allow modification
243 if necessary. The questions and response options distributed to stakeholders are included in
244 the electronic supplementary information (ESI), Table S1a-d. Along with the questionnaire,
245 stakeholders were asked to indicate and rank the three most important criteria for
246 nanomaterial environmental assessment models, regardless of innovation stage
247 considerations.

248

249 The questionnaire was distributed to 60 potential stakeholders targeted within the network of
250 the 24 partner institutes involved in the H2020 project caLIBRAte, and come from sectors
251 including chemical and environmental regulatory bodies; innovators; large and small/medium-
252 sized commercial enterprises; industrial sector bodies; insurers; and consumers. Regulators
253 were specifically included as they directly influence the regulatory frameworks governing the
254 risk assessment of nanomaterials during innovation. Of invitees, 18 (30%) agreed to
255 participate and provide feedback. Most participants agreed to complete the questionnaire as
256 sent, however, some asked to provide verbal feedback in teleconferences both instead of and
257 in addition to filling in the questionnaire. An anonymized overview of the number and type of
258 stakeholders involved and feedback received is presented in Table 1. To maintain
259 confidentiality, specific stakeholders and feedback are reported anonymously throughout this
260 work, according to the numbers assigned in Table 1. All stakeholders gave their informed
261 consent by participating in teleconferences or returning questionnaires. The authors comply
262 with EU and national laws as well as institutional guidelines, including the "Act on Processing
263 of Personal Data" and the "Danish Code of Conduct for Research Integrity" describing data
264 collection, storage and retention.

265 **Table 1.** Overview of the number and type of stakeholders involved and feedback received.

No.	Stakeholder group	Type of feedback	Part(s) of questionnaire addressed	Stage-specific feedback
1	Regulator	Questionnaire	General part	Yes
2		Questionnaire	All	No
3	Industry (Association)	Questionnaire	General part	Yes
4		Teleconference	All	Yes
5	Industry (Large enterprises)	Teleconference	General part	Yes
6		Questionnaire, teleconference	General part	Yes
7		Questionnaire	General part	Yes
8	Consultant	General comments by mail/phone	Not Applicable	No
9		General comments by mail/phone	Not Applicable	No
10		Questionnaire	General part	Yes
11	Industry (SME)	Questionnaire	General part	Yes
12		Teleconference	General part	No
13		Questionnaire	All	Yes
14		General comments by mail/phone	Not Applicable	No
15		General comments by mail/phone	Not Applicable	Yes
16		General comments by mail/phone	Not Applicable	Yes
17		General comments by mail/phone	Not Applicable	Yes
18	Research organization	Questionnaire	General part	Yes

266

267

268 **Identification of relevant nanomaterial environmental assessment models**

269 Considering there are currently more than 500 tools available for nanomaterial safety
 270 assessment³⁰, the present study is delimited to consider the following five categories of
 271 models relevant for environmental risk assessment of nanomaterials:

- 272 1. Material flow models simulating nanomaterial flows into the environment from different
 273 sources and their transport between different environmental compartments
- 274 2. Fate and transport models simulating nanomaterial movement within and between
 275 compartments, and nanomaterial transformations that may affect their state and form in
 276 the environment
- 277 3. Hazard assessment models estimating the effects of nanomaterials on environmental
 278 species
- 279 4. Uptake/bioavailability models assessing nanomaterial uptake and accumulation in
 280 environmental organisms

281 5. Risk assessment models providing estimates for the potential environmental risk of
282 nanomaterials

283
284 Moreover, models/tools described in peer reviewed literature were targeted. In practise,
285 published models/tools relevant to each category were identified through a literature search
286 using Web of Knowledge and Google Scholar, as well as any information from the authors that
287 may identify additional models published in the international or national grey literature
288 (including project progress reports). All identified publications presenting a model/tool/method
289 within these defined categories were included, not just models that had been fully developed
290 into ready-to-use software or tools. In total 38 models relevant for environmental risk
291 assessment were identified, including seven material flow models, eight fate and transport
292 models, seven hazard assessment models, four uptake/bioavailability models and 12 risk
293 assessment models (listed in Table 4). It must be noted that this list is not static over time and
294 not necessarily exhaustive.

295
296 **Development of scoring scheme for models along innovation stages**

297 To allow a systematic assessment of the suitability of different models to different stages
298 (Figure 1), a scheme was designed to score the models against the stage-specific criteria
299 using input from the stakeholder consultation. All identified models were then categorised (cf.
300 categories 1-5 above) and the fit of each model against the features desired by stakeholders,
301 was assessed as exemplified in Table 2 (The full list of assessment criteria are available in
302 Table S2). For this assessment, the primary literature relating to each model was reviewed,
303 and the accordence of the model to the specific identified features recorded. In those cases
304 where the characteristics of each model relevant to a criterion could not be discerned from
305 published information, model owners were contacted to provide details on model format,
306 structure and outputs. Using this approach, it was possible to provide a complete assessment
307 record for each model (not shown).

308

309 **Table 2.** Examples of assessment criteria and response categories for nanomaterial environmental
 310 assessment models (see Table S2 for full list of criteria).

Assessment criteria	Description of criteria	Response categories
Time/cost to parameterise model	What are the maximal costs to calculate and input all of required parameters into the model?	Minutes-Hours, Hours-Day, Days-Weeks, Weeks-Months
Level of expertise	What level of expertise is needed by the user running the model, can it only be operated by experts or is the structure and guidance of sufficient quality that a non-expert would be able to use the tool with minimal training?	Novice, Intermediate, Expert
Time/cost to run model	What is the maximal time running the model may take, including the iterative process or running the model and updating input parameters to gain the desired result?	Minutes-Hours, Hours-Day, Days-Weeks, Week-Months
Approval status	What is the scientific and regulatory approval status of the model, has it been peer reviewed, is it widely used and accepted in the scientific community, has it been the subject of standardisation and/or regulatory approval?	Standardised, Peer reviewed, In development
Format	What is the format of the model, is it available in a stand alone format, is it a web based tool or does it have another non-software format?	Online, Stand alone, Not software
Guidance available	Is there guidance on how to parameterise and operate the model available for potential users?	Yes, No

311
 312 In order to quantitatively rate and compare the suitability of models at different innovation
 313 stages (Figure 1), a scoring scheme was developed, based on the assessment records:

- 314 1. Numerical values were assigned to each assessment criterion and stage combination
 315 to reflect where in the innovation process different model features are suitable. The
 316 large majority of criteria were scored 0, 0.5 or 1 depending on whether they were: not
 317 required/necessary (score 0), desirable/valuable but not essential (score 0.5), or
 318 required/preferred (score 1). Generally, criteria involving greater operational complexity
 319 were assigned higher scores for the later stages where greater resource commitment
 320 is likely to be needed and justifiable.
- 321 2. Three assessment criteria were recognized as being of particular importance based on
 322 the stakeholder feedback; 1) "Time/cost to parameterize the model", 2) "Levels of
 323 expertise needed to operate the model", both of which were applicable to all of the
 324 model types and 3) "Presents comparison of PEC and PNEC" which was relevant only

325 to models in the risk assessment category. For these three “priority criteria” a more
 326 refined set of scoring categories were used whereby models were allocated a score of
 327 0, 0.1, 0.25 0.5, 0.75 or 1.
 328

329 Examples from the scoring scheme are listed in Table 3, with the full scoring scheme available
 330 in the ESI (Table S3). For all the identified models, the features associated with each model
 331 were transformed to numerical values according to the scheme in Table S3. This resulted in a
 332 scoring scheme for each model by stage (not shown).
 333

334 **Table 3.** Examples from the scoring scheme used to assess suitability of nanomaterial environmental
 335 assessment models according to each assessment criteria and stage. The full scoring scheme is
 336 available in the ESI (Table S3).

Criteria		Idea	Scope	Business case	R&D	Test & Validate	Launch	Monitor
Time/cost to parameterise model	Minutes-Hours	1	1	1	1	1	1	1
	Hours-Day	0.5	0.75	1	1	1	1	1
	Days-Weeks	0.25	0.25	0.5	0.5	1	1	1
	Week-Months	0.1	0.25	0.25	0.25	0.5	1	1
Level of expertise	Novice	1	1	1	1	0.75	1	1
	Intermediate	0	0.25	0.5	0.75	1	0.75	0.5
	Expert	0	0	0	0.5	0.75	0.5	0.25
Time/cost to run model	Minutes-Hours	1	1	1	1	1	1	1
	Hours-Day	0	0	1	1	1	1	1
	Days-Weeks	0	0	0	1	1	1	1
	Week-Months	0	0	0	0.5	0.5	0.5	0.5
Approval status	Standardised	1	1	1	1	1	1	1
	Peer reviewed	1	1	1	1	0	0	0
	In development	0.5	0.5	0.5	0	0	0	0
Format	Online	0	0	0	0	0	0.5	0.5
	Stand alone	1	1	1	1	1	1	1
	Not software	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Guidance available	Yes	1	1	1	1	1	1	1
	No	0.5	0	0	0	0	0	0

337

338 Lastly, an algorithm was developed to calculate an overall “assessment score” for each model
339 and stage. The algorithm was specifically designed to make the assessment in a semi-
340 quantitative manner (as it is based on criteria), and calculated in two steps:

- 341 1. For each model and stage, the criteria scores were summed excluding the three
342 “priority criteria”.
- 343 2. To reflect the importance of the priority criteria, these were assigned greater weight in
344 the assessment score calculation. The sum from step 1 was multiplied with the score
345 for each priority criteria in turn. The product values obtained by these three
346 multiplications were then added together and that sum divided by the number of priority
347 criteria that were relevant to each model type, namely two for the material flow, fate
348 and transport, hazard and uptake/bioavailability models (Equation 1) and three for the
349 risk assessment models (Equation 2).

350 Equation 1:

351 Assessment score for each flow/fate/hazard/bioavailability model at each stage =
352 $\sum \text{criteria scores} \cdot (\text{priority criteria 1} + \text{priority criteria 2})/2$

353 Equation 2:

354 Assessment score for each risk assessment model at each stage =
355 $\sum \text{criteria scores} \cdot (\text{priority criteria 1} + \text{priority criteria 2} + \text{priority criteria 3})/3$

356

357 The resulting assessment scores allow comparison of models *within* each of the five model
358 categories (flow, fate, hazard, uptake/bioavailability and risk assessment) to develop ranking
359 lists to identify which models are most suited the requirements of stakeholders for each stage.
360 Comparison of assessment scores *between* model categories was not feasible, as models in
361 this case have different application fields, and hence, can achieve different scores. Moreover,
362 the scoring scale differs between model categories, as not all 41 identified criteria apply to all
363 five categories of models and because the additional priority criterion applies for the risk
364 assessment models.

365

366 **Results and discussion**

367 **Stakeholder requirements along nanomaterial innovation**

368 It proved difficult to achieve the desired stakeholder participation number of 60, as only 30% of
369 invitees agreed to participate. This is, however, consistent with return rates published for user
370 surveys of this type and design.³¹ Also, limited time availability of the stakeholders, resulted in
371 different levels and types of feedback (Table 1), although always based on the generic
372 questionnaire (Table S1a-d). Different approaches and methodologies have been applied for
373 stakeholder elicitations and analysis of feedback.^{25,32} In the present study, the stakeholder
374 feedback was collected as input for the development of the scoring scheme, not for the
375 comparison or weighing of stakeholder views. Therefore, specific stakeholder analysis
376 methodologies as such were not applied, For the sake of transparency, general trends and
377 divergences between stakeholder individuals/groups are discussed in the following.

378
379 In general, the stakeholder (SH) feedback illustrated that the Stage-Gate approach applied in
380 this work (Figure 1) was not always recognized among responders. In some cases, this is
381 because the stakeholder is not directly involved in innovation of nanomaterials and nano-
382 enabled products, as reported by one of the regulators. For other stakeholders, especially
383 small/medium-sized enterprises (SMEs) involved in innovation, development and production of
384 a single nanomaterial product or process, the Stage-Gate system is not applied, although
385 some of the guiding philosophy was clearly recognised. Some stakeholders involved only
386 partly in the innovation process, may be involved only in initial stages, and not the later stages
387 leading to launch (as reported by SH18: a research organization collaborating with SMEs).
388 Others, especially large industrial companies, confirmed that they recognize and use the
389 Stage-Gate approach, although the specific activities and decisions of the various stages and
390 gates may differ from those described within the classic model. For example, SH14, 15 and 16
391 (SMEs) reported conducting legislative safety assessments mainly in the research and
392 development (R&D) stage, whereas SH5 and 6 (large enterprises) reported a focus on the
393 “Test & Validate” stage, or in some cases even in the initial part of the “Launch” stage. Overall,

394 the stakeholder feedback indicates that the middle to late stages (“Business Case”, “R&D”,
395 “Test & Validate”, and “Launch”) are those of primary importance for safety and risk-related
396 work, such as testing, risk assessment and establishing regulatory compliance. Even within
397 these limitations, the majority of responders clearly considered the Stage-Gate model as a
398 suitable framework within which to assess nanomaterial environmental assessment models,
399 as they reported different needs at the different innovation stages in questionnaire responses.

400
401 The stakeholders were asked to indicate one to three of the most important criteria for risk
402 assessment models, regardless of innovation stage. This information was compiled both as
403 requested feedback to questionnaires or from direct discussions in teleconferences. The large
404 industries generally considered the format of the tool, especially whether it is online or stand-
405 alone, as of key importance. The importance of a stand-alone format which can be
406 incorporated into existing company managed systems was stated as being critical, as
407 compared to web-based systems, because it ensures secure handling of confidential
408 information. Compared to the larger corporations, SMEs had greater problems in completing
409 some of the aspects of the needs questionnaire. This was principally due to a lack of in-house
410 experts in safety and regulatory compliance issues, causing them to often hire consultants to
411 undertake such activities. Thus, an easy to operate decision support tool, that clearly lists the
412 data/information needs along Stage-Gates and outlines a simple and easy to parameterise set
413 of data needs and requirement was identified as valuable for SMEs.

414
415 Different stakeholders including regulators, SMEs and a research organization independently
416 reported the need for precautionary measures, i.e. some type of “worst-case scenario”
417 consideration, either during the innovation process; related to any default model values (in
418 case of data gaps) or in the way a model deals with the input data. It was also reported across
419 stakeholder groups that the costs and efforts to run the model must be kept minimal until the
420 R&D stage. This reflects the potential to stop innovation progression after this stage. Low
421 effort in these early stages, thus, encourages innovation, while minimizing resource

422 commitment to the environmental assessment of nanomaterial products that do not enter
423 production. Finally, any regulatory requirements related to the risk assessment of
424 nanomaterials and products need to be incorporated into the system, for example so that the
425 needed input data to run the model rely only on data that are required by regulatory
426 frameworks such as PEC and PNEC data. Indeed, this regulatory compliance was identified
427 as a critical need among almost all responding commercial organisations. Currently, the
428 nanomaterial specific regulatory requirements are being developed and no environmental
429 assessment models have yet been specifically approved. For this reason, although an
430 important criterion, no model currently meets this requirement. Consequently, the assessment
431 reported here develops quantitative information to allow the selection of models to fit this need,
432 rather than it being driven by it.

433

434 Several stakeholders reported no or very limited safety activities at the initial stages and SH6
435 (large enterprise) explicitly said that there is no need for risk assessment in the initial “Idea”
436 and “Scope” stages. Still, some stakeholders mentioned the importance of identifying any
437 potential hazard or “red flags” as early as possible during innovation. This issue may be solved
438 through the use of some very simple models capable of providing “red flags”, while still
439 recognizing the limited resources allocated for risk assessment in the initial stages. Models
440 that score highly in these early stages could, therefore, be expected to present features that
441 support easy parameterization and rapid use by non-experts.

442

443 The commonly stated concept of “safe-by-design” that is frequently mentioned in the nano-
444 safety assessment community³³ was not mentioned explicitly by stakeholders suggesting that
445 it is not a major explicit consideration for those actually involved in innovation or product
446 development. However, some stakeholders did indicate a need for early advice to prevent or
447 reduce product-related risks in cases where these are foreseeable. This could include, for
448 example, support in the selection of the final product matrix into which nanomaterials are
449 incorporated early in design (SH12, SME). While a safe-by-design approach could assist in

450 preventing risks related to nanomaterials and nanomaterial-enabled products, in practice this
451 is not a straight-forward task. The underlying identification of the characteristics, related to
452 nanomaterial hazard, exposure, fate, and transport, needed for safe-by-design represents a
453 major knowledge gap in nano-safety research³³.

454

455 **Suitability of environmental assessment models for each innovation stage**

456 The calculated assessment scores for each identified nanomaterial environmental assessment
457 model along the innovation stages in Figure 1 are presented in Table 4, with colours indicating
458 low (red) or high (green) fit of models with the needs and requirements at each stage as
459 expressed by the stakeholders.

460

461 **Material flow models**

462 Available material flow models all have a similar overall structure that combines usage
463 information with flows between different environmental compartments. This results in a broadly
464 similar pattern of scores across successive stages. The assessment score is relatively low in
465 early stages and increases to peak in the “Test & Validate” and “Launch” stages, followed by a
466 slight decline for the “Monitor” stage (Table 4). Being priority criteria and multipliers in the
467 scoring algorithm, the time and expertise needed to run material flow models generally lead to
468 low scoring of the fit to stakeholder needs, especially in the early stages. At later stages,
469 where speed and ease of use are less important, other common model characteristics, such
470 as the flexibility for use for different nanomaterials and products, and the ability to predict
471 nanomaterial concentrations across different media and environmental compartments,
472 increases scores as these are desirable features for such assessment. The score peaks at the
473 “Test & Validate” stage. As this is the critical stage in product development, this is also were
474 the greatest investment of time and engagement of experts in nanomaterials environment
475 assessment is likely to take place. Hence, it is also the stage at which the greatest amount of
476 resources is likely to be committed. In the “Launch” and “Monitor” stages, the main priority
477 changes from initial establishment to product stewardship. Hence, the desire may be to use

478 reduced resources and to use less experienced staff to support a sustained need for
479 continuous assessment, making these more complex models less well suited to these ongoing
480 requirements.

481
482 Across all models, the PFMA Version 1 model³⁴ was consistently the best scoring of the
483 available material flow models. The feature of this model combined the incorporation of
484 complexity, such as inclusion of dynamic and probabilistic assessment and consideration of
485 the movement of nanomaterials to all relevant environmental compartments, with relative ease
486 of use, a key assessment criterion and multiplier in the appraisal. Thus, this later characteristic
487 was, of critical importance in driving the relatively high score given to this model, as compared
488 to less user-friendly models in this category.

489
490 **Table 4.** Assessment scores by innovation stage for identified nanomaterial environmental assessment
491 models. The assessment score colours represent the level of fit between models and stage-specific
492 needs, ranging from low (red) to high (green).
493

Environmental assessment model		Reference	Idea	Scope	Business case	R&D	Test & Validate	Launch	Monitor
MATERIAL FLOW	PMFA	35	1	2	2	8	14	16	13
	PMFA Version 1.0.0	34	4	8	13	18	23	18	16
	DPMFA	36	1	2	2	9	15	17	14
	Spatial-PMFA	37	1	2	2	8	12	14	12
	MFA	38	2	5	10	13	22	17	14
	Tiede et al. 2010	39	3	2	5	9	14	12	10
	LearNano	40	2	4	10	12	18	15	12
FATE	SimpleBox4Nano	14	4	9	15	18	22	17	14
	NanoDUFLOW	41	2	2	4	9	15	12	11
	Rhine model	11	2	2	4	8	14	11	9
	MendNano	42	1	2	2	7	12	14	11
	WSM/WASP7	43	1	2	2	7	13	15	12
	Rhone Model	44	2	2	4	8	14	11	9
	RedNano	45	1	2	2	8	13	15	12
	GWAVA with water quality module	46, 47	2	2	4	9	14	12	10
HAZARD	US EPA SSD Generator	48, 49	2	4	9	13	21	17	14
	SSWD	10	1	1	2	8	13	14	12
	NanoQSAR model	50, 51	7	8	12	14	14	11	9
	Framework for oxidative stress potential	52	8	7	6	10	9	6	4
	nanoSAR	53	4	5	6	10	9	6	4
	nano-SAR (OCHEM, WEKA)	54	2	2	5	9	13	10	8
	Nanoprofiler 1.2	55	2	2	4	9	13	10	8
UPTAKE	Kinetic model/BCF	56	6	11	16	17	16	12	10
	Two component Efflux/uptake model	57	6	11	16	17	16	12	10
	Biodynamic model	58	6	11	16	17	16	12	10
	BLM concept model	59	6	11	16	17	16	12	10
RISK	FINE	60	6	6	8	12	14	15	13
	Precautionary Matrix for Synthetic Nanomaterials	8	22	20	19	17	13	14	13
	Tervonen et al. 2009	61	8	9	15	16	18	14	13
	SUN, 2016	34	7	8	14	20	27	23	21
	pERA	13	6	6	9	16	20	21	19
	LICARA nanoSCAN	9	9	11	14	16	16	13	11
	nanoinfo	62	6	6	10	17	25	22	19
	Topuz and van Gestel, 2016	63	5	6	8	16	19	20	18
	GUIDEnano tool	None	6	6	10	18	26	22	20
	SUNDS 2 nd tier	None	5	5	9	17	25	22	20
	SUNDS 1 st tier	9	9	11	14	16	16	13	11
	GUIDEnano tool intermediate	none	8	11	18	23	28	23	21

496 **Environmental fate and transport models**

497 The environmental fate and transport models followed a similar pattern of scoring across
498 stages as the material flow models, with lower scores in early stages. The common pattern in
499 scores between the different fate and transport models across stages reflects a common set of
500 shared features. These include representations of key nanomaterial processes, such as homo-
501 and heteroagglomeration, sedimentation, and dissolution, as the major features driving fate
502 and transport, especially in aquatic environments. With a number of relatively complex
503 features, these models are often rather time-consuming to parameterise and operate and also
504 require a high level of expertise to identify parameters and interpret outputs. This translates to
505 relatively poor scores in the earlier stages, whereas in later stages where increase resource
506 investment is more often warranted, the penalty arising from the required resource
507 commitment reduces and scores consequently rise (Table 4).

508
509 The SimpleBox4Nano model^{12,14} scores the highest of the fate and transport models across all
510 stages. Indeed the calculated scores for SimpleBox4Nano are in some cases two-times higher
511 or more than those awarded for any of the alternative fate and transport models in some
512 stages (e.g. “Scope” and “Business case”). The key characteristics underlying the higher
513 scores achieved for SimpleBox4Nano include its open availability for use, full guidance
514 availability, and estimation of nanomaterial fate and transport across a range of environmental
515 compartments (air, soil, water and sediment). The model is Excel-based and, hence, requires
516 a lower level of expertise than some of the other models presented in code-based formats. As
517 a critical assessment multiplier, this relative ease of use has a major impact on the Stage-Gate
518 scores.

519

520 **Uptake and bioavailability models**

521 To date, only few models have been proposed for modelling the uptake and bioavailability of
522 nanomaterials in ecological assessments, as methods for such studies remain in their relative
523 infancy. One of these models is the biotic ligand model (BLM), which has been widely used for

524 modelling metal bioavailability. It has recently been proposed for use with silver nanoparticles
525 in initial studies, although challenges have been identified.⁵⁷ Also, three toxicokinetic modelling
526 approaches are included in this category; “Kinetic model/bioconcentration factor”, “Two
527 component efflux/uptake model”, and “Biodynamic model”, which are all based on modelling
528 the influx/uptake and efflux/elimination of nanomaterials for organism tissues to consider
529 bioaccumulation. The use of bioaccumulation factors requires equilibrium partitioning, which is
530 not considered relevant for nanomaterials, due to the kinetic nature of many processes
531 affecting internal fate, such as attachment, dissolution, and chemical transformation.²¹ Rather
532 than a single model, these approaches all represent a family of models with different
533 complexities. For example, they may consider the organism as one or more compartments in
534 the model, depending on available information on internal anatomy and metal handling
535 characteristics. Only the BLM is designed to consider speciation and bioavailability. Thus, a
536 significant research gap remains in this area.

537
538 The four models are awarded the same scores across stages. Scores are low in the early
539 stages, driven primarily by a somewhat restricted scope and range of settings in which these
540 models can currently be used, in addition to intermediate or high level of expertise needed to
541 parameterize and run each model. In the “Business case” and “R&D” stages, scores increase
542 as the greater resource requirements mean the requirements of time and expertise is no
543 longer extensively penalised. In later stages, scores decline again as the models lack
544 considerations of nonspecific properties. Hence, it remains uncertain whether they will fully
545 capture the characteristics of a nanomaterial affecting bioaccumulation. Indeed initial efforts to
546 use the BLM for nanomaterials have recognized problems, such as the potential for exposure
547 to occur through ingestion, which is an exposure route not routinely considered in this model
548 structure.^{57,64}

549

550 **Environmental hazard models**

551 Seven environmental hazard models relevant for use with nanomaterials were identified,
552 covering two main approaches;

- 553 1) Species sensitivity distribution (SSD) models that estimate the hazardous concentration
554 for a certain percentage of species based on the distribution of toxicity data from
555 laboratory field tests (or potentially field based assessments).
- 556 2) Quantitative structure activity relationship (QSAR) models that aim to predict the toxicity
557 of untested nanomaterials based on chemical/structural descriptors.

558 In environmental risk assessment, both SSD and QSAR models are essential components of
559 current regulation as they can extrapolate from known data to untested species and
560 substances. Given the number of different nanomaterials that can be produced from
561 combinations of core chemistry, size, shape, surface functionalization etc., and the need to
562 protect the range of untested species in ecosystems, such extrapolation models are likely to
563 remain an important component of any future nanomaterial management system.

564
565 Of the two SSD tools available, the US EPA SSD generator scored higher than the “species
566 sensitivity weighted distribution” (SSWD) approach in all stages. This is driven by the relative
567 ease of the US EPA tool compared to the SSWD, which is more complex and time-consuming,
568 as besides species sensitivity, it also considers species relevance, trophic level abundance
569 and the level of nano-specific characterisation accompanying the toxicity data. This greater
570 level of complexity could be warranted in later stages as these considerations can benefit from
571 a more complete assessment. However, even though the scores for both tools do rise along
572 stages, the US EPA tool always outscores the SSWD tool based on ease of use weighting.
573 However, given the efforts that may be committed to assessments at this stage, this outcome
574 may not preclude the selection of more complex tools for later stages if deemed appropriate.

575
576 The five QSARs identified apply various approaches to use nanomaterial properties and
577 features as predictors of effects, either on biochemical related endpoints, such as oxidative
578 stress potential, or on measured endpoints such as cell viability. These models generally

579 require a high level of expertise to operate, as they require input of a range of nano-specific
580 properties that are both difficult to derive and complex to interpret and ultimately parameterise.
581 Consequently, all nanoQSAR models score rather low in all stages. A common feature of the
582 nanoQSAR models is that the score does not greatly increase towards later stages (i.e. the
583 rise in the score for each model is less pronounced than for other model types). Because they
584 make use of prior information in the absence of specific hazard information, nanoQSAR
585 models are most applicable to assessment in the early developmental stages, where
586 stakeholders expressed a clear demand for early “red flags” relating to potential hazard. This
587 is similar to the QSAR strategies applied for organic chemicals. Hence, although they clearly
588 require development, especially relating to the ease of use, there remains a potential role for
589 reliable nanoQSAR models in environmental risk assessment. Among nanoQSAR models, the
590 method of Puzyn et al. (2011) received the highest score. The model is designed to predict the
591 bacterial toxicity of metal oxide nanoparticles based on a single descriptor; their enthalpy of
592 formation of a gaseous cation having the same oxidation state as that in the metal oxide
593 structure. This is to date, the most well-known and established nanoQSAR. It is, however,
594 restricted in its domain being applicable only to metal and metal oxide nanomaterials; suitable
595 for predicting effects only for materials with different pristine core chemistry (and not variations
596 in properties such as size, shape, and coating); and applicable only for the bacterial species
597 with which it was developed. Expanding the domain space of nanoQSAR models is, thus,
598 recognised as a research priority. For all hazard models, the issue of data availability are an
599 additional uncertainty. This means that models may be assessed fit for purpose, although
600 adequate data may not be available to actually run them.^{65,66}

601

602 **Environmental risk assessment models**

603 The environmental risk assessment models comprise both the hazard and exposure
604 assessment of nanomaterial related risks. In total 12 tools were identified, ranging from
605 screening levels methods (e.g. LICARA nanoSCAN, Precautionary Matrix for Synthetic
606 Nanomaterials), to complex tools covering all aspects of fate and transport, and hazard

607 assessment, e.g. the GUIDEnano tool and the SUN discussion support tool (SUNDS). A
608 particular challenge when assessing the risk assessment models was that some contain
609 different material flow, fate and transport, and hazard assessment tools embedded within their
610 overall structure. For example, the SUNDS tool include the LICARA nanoSCAN (named 1st tier
611 in the results section) and the pERA developed by Gottschalk et al. in 2013¹³, whereas the
612 LICARA nanoSCAN includes parts of the Precautionary Matrix for Synthetic Nanomaterials⁸,
613 NanoRiskCat⁶⁷ and StoffenManager Nano⁶⁸. As a result, the tools can be used in different
614 ways. This creates a specific challenge regarding the scoring of model features, such as ease
615 of use and functionality. Similarly, many risk assessment tools include different methods for
616 estimating hazard including SSDs. When this is the case, models may be well suited for
617 particular criteria, i.e. they may take different nanomaterial properties into account. However,
618 the use of an SSD module that does not account for nano-specific properties may mask the
619 value of such features, if a lack of consideration of nano-specific features in the hazard module
620 influences the overall model score. It should be noted that several tools are not yet fully
621 developed and may differ in later versions to be released. Additionally, we differentiated
622 GUIDEnano into GUIDEnano and GUIDEnano-intermediate that accounts for the user
623 experience by recommending default values.

624
625 Score comparison between models along stages indicated that principally, the ERA tools can
626 be differentiated into two categories: applicable to early stages and applicable to late stages.
627 Three tools, the Precautionary Matrix for Synthetic Nanomaterials, the LICARA nanoSCAN
628 and SUNDS 1st tier (equal to LICARA nanoSCAN), score higher than other models in the
629 earlier stages. These tools apply a risk screening (Precautionary Matrix) and risk-benefit
630 assessment (LICARA/SUNDS 1st tier) to nanomaterials evaluation. Such screenings require
631 less data and information about the nanomaterial allowing the (unexperienced) user to apply
632 these tools easily and with minimal time requirements. The results of these tools indicate
633 where further investigations or information are required to proceed further in the stages. By
634 doing so, such methods apply a less evidence-driven approach to assess potential risks and

635 benefits without achieving a complete risk assessment. These tools scored lower in the later
636 stages due to the increasing demands on evidence of data and information, which is
637 accompanied by the need for expert knowledge and more time-consuming and comprehensive
638 assessments.

639
640 The remaining nine risk assessment models each score lower in the early stages, driven
641 predominately by the need for expert parameterisation and relative high time requirements for
642 successful parameterisation and operation. The majority of these models peak in the “R&D”
643 stage before declining slightly. Among these models, the GUIDEnano-intermediate tool
644 version scored the highest in the “R&D” and “Test & Validate” stages as it provides a pre-
645 parameterized tool for intermediate users, while the SUNDS tool only gives (and learns) by
646 scenarios entered into the tool. In the end, both tools may be on the same score level
647 depending on how well the database is managed and updated. Although the scores are
648 similar, differences are found in the possibilities to adjust environmental compartments and
649 regions (i.e. GUIDEnano) and the determinations of PEC values for the complete range of
650 applications (SUNDS) vs. the contribution of a single application to the PEC (GUIDEnano).
651 Also, the data handling and evaluating of data in GUIDEnano is more guided than in the
652 SUNDS tool. A challenge for the evaluation of the nanoinfo tool, was obtaining information on
653 how the algorithms work behind the web interface. Here, we used the published articles that
654 constitute the modules of the tool. Particularly, the hazard assessment module is still being
655 developed to apply QSARs for hazard assessment. However, it must be stressed that for the
656 mentioned tools development is ongoing and the evaluation should be repeated in the future.

657

658 **Conclusions**

659 We evaluated the fit of 38 models relevant for assessing the fate, exposure, hazard or risk of
660 nanomaterials to the innovation stages, considering 41 criteria reflecting needs and
661 requirements obtained by consultations with 18 stakeholders of six different groups.

662 Important stakeholder criteria for environmental risk assessment models include the required
663 time/costs and level of expertise needed for model parameterisation and operation. For risk
664 assessment models specifically, also the generation of PEC/PNEC was a key requirement. All
665 stakeholders identified regulatory compliance as a critical criterion, which is presently difficult
666 to incorporate into models as frameworks for nanomaterial risk assessment has yet to be
667 developed and adopted. Also, the availability of data to run the models is a prevailing issue for
668 nanomaterials. Consequently, the generation of model input data and development of
669 regulatory requirements for nanomaterials will likely have a significant influence on the future
670 selection as well as development of tools.

671 Within the five model categories, similar model features often resulted in similar scoring
672 profiles across stages. The majority of models are relatively complex tools developed by
673 experts for use in a research context and, therefore, generally score higher at later stages
674 where the greatest amount of resources and expertise are allocated during product innovation.
675 This is driven by the stakeholder requirements to limit investments in risk management to the
676 stages after initial innovation but prior to “Launch”. Models requiring less time and user
677 expertise, such as nanoQSARs and the less complex risk assessment models, fit stakeholder
678 needs for early stages, as they aim to identify potential hazards and provide risk management
679 measures, without substantive early resource investments. Refinement of tools over the next
680 few years may change the balance in scoring and assessment between particular tools. A
681 flow-through from research tools to simplified and easily operationalized systems may
682 ultimately deliver the balance between rigor and ease that is needed.

683

684 **Conflict of interest**

685 There are no conflicts to declare.

686

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696

697

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