Reviewer Guidance

Integration of Study Results to Assess Concerns about Human Reproductive and Developmental Toxicities

DRAFT GUIDANCE

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Pharmacology/Toxicology

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U.S. Department of Health and Human Services
Food and Drug Administration
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Pharmacology/Toxicology

TABLE OF CONTENTS

1 # Reviewer Guidance[1]

2

3 # Integration of Study Results to Assess Concerns about
4 # Human Reproductive an

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6 # Developmental Toxicities

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12
13 This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's)
14 current thinking on this topic. It does not create or confer any rights for or on any person and does
15 not operate to bind FDA or the public. An alternative approach may be used if such approach
16 satisfies the requirements of the applicable statutes and regulations.
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23 ## I. INTRODUCTION

24
25 This draft guidance describes a process for estimating the increase in human
26 developmental and reproductive risks as a result of drug exposure when definitive human
27 data are unavailable. The overall approach integrates nonclinical information from a
28 variety of sources (i.e., reproductive toxicology, general toxicology, and toxicokinetic
29 and pharmacokinetic information, including absorption, distribution, metabolism and
30 elimination findings) and available clinical information to evaluate a drug's potential to
31 increase the risk of an adverse developmental or reproductive outcome in humans.
32
33 The integration process focuses on the likelihood a drug will increase the risk of adverse
34 human developmental or reproductive effects. It does not consider the nature (e.g.,
35 severity, reversibility or repairability) of the adverse response, or otherwise consider the
36 clinical implications of the response. These risk management issues will be discussed in
37 separate guidance on how to address the clinical implications of developmental and
38 reproductive risks in product labeling. Because of inherent differences between drug and
39 biological products, and resulting differences in the types of preclinical data collected for
40 drug and biological products, the process described in this guidance will often not be
41 useful in evaluating potential adverse reproductive or developmental effects for

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[1] This guidance has been prepared by the Office of Review Management in the Center for Drug Evaluation
and Research (CDER) at the Food and Drug Administration (FDA).

42   biological products. However, the general principles described (i.e., a comprehensive
43   analysis of available data) will typically be of some relevance to biological products.[2]
44
45
46   **II.**   **BACKGROUND**
47
48   **A.**   **Data Needed to Use the Integration Process**
49
50   Ordinarily, the integration process should be based on an evaluation of a complete
51   set of the expected general toxicology, reproductive toxicology, and
52   pharmacokinetics studies.[3] This evaluation should include an assessment of the
53   ability of the drug to produce a positive finding in the relevant animal studies
54   (e.g., whether doses used were large enough to induce toxicity of some kind).
55   The evaluation should also compare animal and human pharmacodynamic effects,
56   animal and human metabolism and disposition, animal and human pharmacologic
57   and toxic effects, and drug exposures in animal studies in relation to the highest
58   proposed dose in humans.
59
60   The type and extent of available toxicology data may vary depending on the
61   biological actions of the product, test systems available for studying the
62   compound, and other factors. In some cases, the data will not include all
63   desirable general toxicology, reproductive toxicology, and pharmacokinetics
64   studies. In some of those cases, it may still be possible to use the integration
65   process without all the desired information. In other cases, limited available data
66   will preclude the use of the integration process (e.g., often the case for biological
67   products). Even if the integration process cannot be used, the product should be
68   evaluated to the greatest extent possible in accordance with sound scientific
69   principles and the considerations described in this document.
70
71   **B.**   **Types of Reproductive and Developmental Toxicity Evaluated**
72
73   For purposes of this document, there are two broad categories of toxicity —
74   reproductive and developmental toxicity — and, within those categories, seven
75   classes of toxicity. In the reproductive toxicity category there are three classes of
76   toxicity: toxic effects on *fertility, parturition*, and *lactation*. In the developmental
77   toxicity category there are four classes of toxicity: *mortality, dysmorphogenesis*
78   *(structural alterations), alterations to growth,* and *functional toxicities.* For a
79   given drug, each class of toxicity should ordinarily be assessed. A positive signal
80   in any class of reproductive or developmental toxicity, whether in valid

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[2] Although this is not a joint CDER/CBER guidance, CBER was consulted during guidance development. For more information, contact the Division of Clinical Trials Design and Analysis.

[3] See the following International Conference on Harmonisation (ICH) guidances for industry: *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals; S3A Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies; S5A Detection of Toxicity to Reproduction for Medicinal Products;* and *S5B Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility*.

81 reproductive or general toxicology studies or from human use studies, should be
82 evaluated using the process described in this guidance to estimate the likelihood
83 of increased reproductive or developmental risk for humans (see discussion of the
84 integration process in Section III and schematic representation of the process in
85 Figure C).

86   *1.   Reproductive Toxicities*

87

88 Reproductive toxicities include structural and functional alterations that
89 may affect reproductive competence in the F_0 generation. The three
90 classes of reproductive toxicity include effects on fertility, parturition, and
91 lactation.

92

93 • Fertility

94

95 Male reproductive toxicity associated with administration of a drug may
96 be seen as degeneration or necrosis of the reproductive organs, reduction
97 in sperm count, alterations to sperm motility or morphology, aberrant
98 mating behavior, altered ability to mate, alterations to endocrine function,
99 or overall reduction in fertility.

100

101 Female reproductive toxicity may be seen as damage to the reproductive
102 organs, alterations to endocrine regulation of gamete maturation and
103 release, aberrant mating behavior, altered ability to mate, or overall
104 reduction in fertility. Diminished fertility in female animals is typically
105 detected by reductions in the fertility index, the number of implantation
106 sites, time to mating, or fecundity.

107

108 • Parturition

109

110 Toxicities affecting labor and delivery in animals may be seen as changes
111 in the onset or duration of parturition. Changes in the duration of
112 parturition are frequently reported as mean time elapsed per pup, or total
113 duration of parturition.

114

115 • Lactation

116

117 Drugs administered to lactating animals may be a source of unwanted
118 exposure in the nursing neonate, may alter the process of lactation in the
119 nursing mother (e.g., the quality or quantity of milk), or may alter
120 maternal behavior towards the nursing offspring.

121

122   *2.   Developmental Toxicities*

123

124 Developmental toxicities are generally those that affect the F_1 generation.
125 The four classes of developmental toxicity are mortality,

126   dysmorphogenesis (structural alterations), alterations to growth, and
127   functional toxicities.

128

129   •   Mortality

130

131   Mortality due to developmental toxicity may occur at any time from early
132   conception to post-weaning, ("embryo-fetal death" is a subset of mortality
133   due to developmental toxicity). Thus, a positive signal may appear as pre-
134   or peri-implantation loss, early or late resorption, abortion, stillbirth,
135   neonatal death or peri-weaning loss.

136

137   •   Dysmorphogenesis (Structural alterations)

138

139   Dysmorphogenic effects are generally seen as malformations or variations
140   to the skeleton or soft tissues of the offspring, and are commonly referred
141   to as *structural alterations*.

142

143   •   Alterations to Growth

144

145   Alterations to growth are generally seen as growth retardation, although
146   excessive growth or early maturation may also be considered alterations to
147   growth. Body weight is the most common measurement for assessing
148   growth rate. Crown-rump length, and ano-genital distance may also be
149   measured.

150

151   •   Functional Toxicities

152

153   Functional toxicities could include any persistent alteration of normal
154   physiologic or biochemical function, but typically only developmental
155   neurobehavioral effects and reproductive function are measured.
156   Common assessments include locomotor activity, learning and memory,
157   reflex development, time to sexual maturation, mating behavior, and
158   fertility.

159

160

161 **III.**   **DISCUSSION**

162

163   The complete data integration process is schematically presented in Figures A-C,
164   which are attached to this document. To clarify the manner in which data should
165   be passed through the integration process, the process has been divided into three
166   components, which are discussed in the following sections A-C. Briefly, Figure
167   A is applicable to all data-sets, while Figure B is applicable only to data-sets
168   without evidence of reproductive or developmental toxicity. Figure C is
169   applicable to data-sets with positive indications of reproductive or developmental
170   toxicity.

171

172 **A.   Overall Decision Tree (Figure A).**

173

174   The decision tree process outlined in Figure A at the end of the document, should

175   be used *for each of the seven classes of reproductive or developmental toxicity*

176   discussed in Section II.B. For a given drug, studies may have been conducted to

177   evaluate potential effects on none, some, or all of the classes of reproductive and

178   developmental toxicity. Where studies are available for any of the different

179   classes, the outcome may be one or more positive signals, or no signal. It is

180   recognized that in practice one study may address several classes of toxicity and

181   that a study may be considered adequate to evaluate all, some, or none of the

182   classes of toxicity addressed.   Figure A depicts the sequential decisions that

183   should be made in evaluating the various situations that may be encountered and

184   the next steps that should be taken where there are evaluable studies with positive

185   or negative findings.

186

187   *1.   Availability of Studies*

188

189   In Figure A, the first question that should be asked for each class of

190   toxicity is: "Were studies performed that are relevant to an assessment of

191   the risk of that class of reproductive or developmental toxicity in humans

192   and are the detailed study results available for comprehensive evaluation?"

193

194   If no studies were conducted, or detailed study results are unavailable for

195   comprehensive evaluation, the review should explain that studies adequate

196   to assess the risk of that class of toxicity were not done, or are otherwise

197   unavailable. In such circumstances, risk to humans is considered *unknown*

198   or *not evaluable* and the product labeling should reflect that conclusion:

199

200   **Example: The risk of [class of reproductive or developmental**

201   **toxicity] with [Drug X] is unknown. There are no data to**

202   **evaluate its potential to cause [class of reproductive or**

203   **developmental toxicity].**

204

205   If studies were conducted and are available for comprehensive evaluation,

206   the assessment process should continue with question 2.

207

208   *2.   Relevance of Studies*

209

210   The next question that should be asked for each class of toxicity is: "Do

211   the studies done provide information relevant to assessing the risk of that

212   type of reproductive or developmental toxicity for the proposed human

213   use?" If the test system was not relevant, the review should explain why

214   the studies were not relevant or otherwise appropriate (i.e., inappropriate

215   test protocol or species, nonrelevant route of drug administration[4]) and

---

[4] This may also apply to information from humans in which the route is inappropriate to provide relevant
information for the clinical indication.

216 should discuss all supporting information that bears on study relevance. If
217 the test system was not relevant, the risk to humans is considered *unknown*
218 or *not evaluable* and the product labeling should reflect that conclusion:
219
220 **Example: The risk of [class of reproductive or developmental**
221 **toxicity] with [Drug X] is unknown. There are insufficient**
222 **data to evaluate its potential to cause [class of reproductive or**
223 **developmental toxicity].**
224
225 If the studies conducted are relevant to evaluating the risk of the particular
226 class of toxicity in humans, the risk integration process should continue
227 with question 3. Note that the processes in Figures B and C (see end of
228 document) are intended to be used only when studies are considered
229 adequate to assess the specified risk. They should not be used to evaluate
230 findings (positive or negative) derived from inadequate studies.
231
232 *3.   Presence or Absence of a Signal*
233
234 If the test system is relevant and appropriate for assessing the risk of
235 toxicity in humans, the next question that should be asked for each class of
236 toxicity is "Was there a positive signal (suggesting toxicity)?" If no signal
237 was seen, the evaluation process should continue per Section B (Figure B
238 at end of document). If a positive signal was seen, the evaluation process
239 should continue per Section C (Figure C at end of document).
240
241 **B.   No Signal (Figure B)**
242
243 Where there is no positive signal for one of the seven classes of reproductive or
244 development toxicity, the risk assessment should be a step-wise process leading to
245 a recommendation about the relevance of the nonfinding in humans. A graphic
246 representation of this process is presented in Figure B (see end of document).
247
248 If multiple studies are available to assess a class of reproductive or developmental
249 toxicity (e.g., multiple studies would be expected for the evaluation of
250 dysmorphogenic effects - ICH stage C), the process in Figure B should be used
251 only if the results of all studies relevant to a particular class of reproductive or
252 developmental toxicity are negative for that type of toxicity. If any study (general
253 toxicity, reproductive, or developmental toxicology study) has a positive signal
254 for that class of reproductive or developmental toxicity, the process in Section C
255 (Figure C) should be used.[5]
256
257 The following four factors should be considered during the evaluation of each
258 class of reproductive or developmental toxicity for which there was no signal.
259

---

[5] Studies with conflicting signals and inter-study *concordance* and *nonconcordance* are addressed in Section C.

260   *1.*   *The Model/Test Species Predictive Adequacy*

262   To what extent are the models or test species used likely to be predictive

263   of human response? The following questions bear on the determination of

264   a model's predictive adequacy.

266   • Do any of the models or test species (or systems) demonstrate or have

267   the capability of responding to the pharmacodynamic effect(s) of the

268   drug?

270   • Do any of the model/test species (or systems) demonstrate an overall

271   toxicity profile that is relevant to the human toxicity profile?

273   • Do any of the model/test species (or systems) demonstrate

274   pharmacokinetic (including ADME) profiles for the drug that are

275   qualitatively similar to those in humans?

277   If the responses to these questions suggest that the response of the test

278   species is of little relevance to humans, the review should explain why the

279   animal study or studies conducted with the drug may not be fully adequate

280   to evaluate the risk for the particular class of toxicity in humans (i.e., why

281   the test may have low predictive value). Even if the test system is

282   determined to be of limited relevance, the review should consider the

283   remaining factors (2-4 below) and describe any additional uncertainties.

285   *2.*   *Adequacy of Study Doses and Exposure*

287   The following elements should be considered in assessing the relevance to

288   humans of the drug doses and exposure in the test system:

290   • Were adequate doses (concentrations) of the drug administered to the

291   test species or test systems (e.g., MTD, MFD)?

293   • Were the exposures (based on AUC, C_{max}, or other appropriate

294   systemic exposure metric) achieved in the test species or test systems

295   adequate relative to those demonstrated in humans at the maximum

296   recommended human dose?

298   If the answer to either of these questions is no, the evaluation should state

299   that the animal studies conducted may be inadequate to fully evaluate the

300   risk for the particular class of toxicity reported to be negative and explain

301   in detail why they may be inadequate. Even if the study doses and

302   exposure are considered inadequate, the evaluation should proceed to the

303   remaining sections (3-4 below), and any additional uncertainties should be

304   described.

306		*3.* *Class Alert*
307		
308		Class alerts should be based on adverse reproductive or developmental
309		effects previously demonstrated in humans by closely related chemical
310		entities or compounds with similar pharmacodynamic effects. If there is a
311		Class Alert for the drug, based on a related chemical structure of parent or
312		metabolite or related pharmacologic effect, the class-specific information
313		relevant to the class of toxicity reported to be negative should be included
314		in the risk evaluation and discussion of the drug. The basis for the class
315		alert for adverse effects in humans should be reasonably applicable to the
316		drug being evaluated.
317		
318		*4.* *Signals for Related Types of Reproductive and Developmental*
319		*Toxicity*
320		
321		The next step in evaluating the relevance of a no signal finding for a
322		particular class of reproductive or developmental toxicity is to assess
323		findings for related reproductive and developmental toxicities. A positive
324		signal for one class of toxicity may suggest some risk in humans for other
325		toxicities in the same category for which there were no findings in
326		animals. The issue of related toxicities is most relevant for developmental
327		toxicities. For example, if there is no signal for fetal mortality, but a
328		positive signal for alterations to growth or dysmorphogenesis in one (or
329		more) animal species, it may be inappropriate to conclude there is no risk
330		of fetal mortality for humans. Related toxicities may also be relevant for
331		reproductive toxicities where a hormonal mechanism is identified, the
332		mechanism could be relevant to multiple aspects of reproductive
333		performance, and the mechanism is relevant to humans.
334		
335		If positive signals for related classes of toxicity were observed in the
336		animal studies, the evaluation should state that there was no observed
337		effect on the type of toxicity being assessed, but positive signals were seen
338		for related toxicities. If there is no positive signal for any class of
339		reproductive or developmental toxicity, the evaluation should state that
340		there is no expected increase in risk for reproductive or developmental
341		toxicity in humans based on the results of animal studies.
342		
343	**C.**	**One or More Positive Signals (Figure C)**
344		
345		*1.* *Overview of the Integrative Process*
346		
347		There are six factors that may affect the level of concern for a positive
348		signal in any of the classes of reproductive or developmental toxicity: (1)
349		signal strength part I, (2) signal strength part II, (3) pharmacodynamics,
350		(4) concordance (metabolic and toxicologic concordance to the human);
351		(5) relative exposure; and (6) class alerts. As described in more detail
352		below, the integration tool considers signal strength in two different ways,

353	so signal strength is treated as two separate factors. Each factor has
354	several contributory elements. The outcomes of the analyses of these six
355	factors are used in the six columns in the integration tool (see Figure C).
356	Human data may be considered separately from nonclinical findings and
357	may greatly influence the overall assessment of human risk of
358	reproductive or developmental toxicity.
359	
360	The overall integrative analysis begins with a positive signal in a class of
361	reproductive or developmental toxicity in one or more of the examined
362	species. The positive signal may be from a reproductive or developmental
363	toxicology study or an effect observed on a reproductive tissue, system, or
364	behavior in a general toxicology study. Each of the six factors should be
365	analyzed independently. Guidance is provided on what types of
366	observations for each of the six factors might increase, decrease, or leave
367	unchanged the level of concern for that factor. These analyses should not
368	be an arithmetic summation of the contributing elements within each
369	factor, but a weighted integration that takes into account the quality and
370	nature of the data under consideration. The assessments of concern for
371	each of the six factors should be assigned values of +1, -1 or 0,
372	respectively, if the factor is perceived as increasing, decreasing, or leaving
373	unchanged the level of concern for a class of reproductive or
374	developmental toxicity. Conclusions from the six analyses should be
375	summed to arrive at a comprehensive evaluation of the potential increase
376	in risk for each class of the seven reproductive or developmental classes
377	for which there was a positive signal.
378	
379	2. *A Note on Intra- and Inter-Species Concordance*
380	
381	Intra- and interspecies concordance of adverse effects in animals deserves
382	some special consideration in this risk integration process. Positive
383	signals in related types of reproductive or developmental toxicity within
384	the same species indicates intra-species concordance of effects (e.g., a
385	reduction in normal growth and an increase in developmental mortality).
386	Positive signals for the same or a related type of toxicity across species
387	indicates interspecies concordance. In general, findings for which there is
388	intra- or interspecies concordance are more convincing than a positive
389	signal in only one toxicity class in only a single species.
390	
391	In evaluating potential human risk for adverse reproductive or
392	developmental outcomes, if there is interspecies concordance for a single
393	adverse effect it may be reasonable to conclude that a similar effect is the
394	most likely adverse event to be seen in humans treated with the drug. If
395	different but related adverse effects are seen in multiple test species (e.g.,
396	alterations to growth in one species and developmental mortality in
397	another, or parturition effects in one species with lactation effects in the
398	second), it may be reasonable to assume there is some level of risk for
399	categorically related endpoints in humans.

400
401 A detailed discussion of the overall integrative analysis, the six
402 individual factors, the contributory elements for each factor, and the
403 assignment of the level of concern for each factor is presented in
404 Sections 1-6**.**
405
406 a. Signal Strength, Part I
407
408 For the first signal strength factor, a positive signal in any reproductive
409 or developmental toxicity class should be analyzed with respect to
410 three contributory elements that examine whether the finding is
411 present in more than one setting: (a) whether there is cross-species
412 concordance (where more than one species has been studied), (b)
413 whether there is multiplicity of effects, and (c) whether adverse effects
414 are seen at more than one time.
415
416 **Cross-Species Concordance**
417
418 The defining characteristic of cross-species concordance is a
419 positive signal in the same class of reproductive or developmental
420 toxicity in more than one species. Cross-species concordance is
421 most likely to be identified for structural abnormalities
422 (dysmorphogenesis) or developmental mortality because these
423 toxicities are frequently detected in the *organogenesis* testing
424 paradigm, in which multiple species are typically evaluated. In
425 addition, alterations to endocrine function or gonadal
426 histopathology (which may alter fertility) may be indirectly
427 detected in subchronic and chronic toxicity studies in rodents and
428 nonrodents. When cross-species concordance is observed, there is
429 increased concern for reproductive or developmental toxicity in
430 humans. In contrast, there is decreased concern when a signal is
431 detected in only one species (with the proviso that the negative
432 species is an appropriate animal model and the studies were
433 adequate in design, dosing, and implementation).
434
435 For alterations to parturition or lactation, it's often not possible to
436 assess cross-species concordance because peri- and postnatal studies to
437 assess these classes of toxicity are usually done in only a single
438 species.
439
440 **Multiplicity of Effects**
441
442 Multiplicity of effects refers to observation, in a single species or
443 animal model, of two or more positive signals within one of the two
444 general categories of toxicity (reproductive or developmental) or
445 within one of the seven classes of reproductive or developmental

446	toxicities. The observation of increased embryo-fetal death and
447	structural abnormalities (dysmorphogenesis) in an animal test species
448	is an example of multiple positive signals within a general category.
449	The observation of two or more positive signals for structural
450	abnormalities in tissues of multiple embryonic origin (e.g., defects
451	affecting soft tissue, skeletal tissue, and/or neural tissue) is an example
452	of multiple positive signals in a toxicity class.
453	
454	If all species examined demonstrate multiplicity of effects, there is
455	increased concern for reproductive or developmental toxicity in
456	humans. If there are positive signals in two or more species, but
457	multiplicity of effects is observed in only one species, concern is
458	unchanged for this element. If no species studied exhibits multiplicity
459	of effects, there is decreased concern.
460	

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**Adverse Effects at Different Stages
of the Reproductive or Developmental Process**

</div>

461	
462	
463	
464	Evidence of toxicity may arise during any stage of the reproductive or
465	development process. For example, developmental mortality may be
466	reported as early or late resorptions, abortions, or stillbirths. If a positive
467	signal in animals is observed in multiple stages of development, there is
468	generally greater concern for adverse human reproductive outcomes. If a
469	positive signal is observed only during a single, discreet interval, the level
470	of concern is unchanged. If the positive signal occurs only during
471	processes that are of limited relevance to humans (rare), there would be
472	less concern for adverse human reproductive outcomes. In addition to its
473	relevance to this evaluation process, it is also important to define the
474	timing of the period of susceptibility for the observed positive signal to
475	provide a context for the human risk.
476	
477	b. Signal Strength, Part II
478	
479	In assessing the second signal strength factor, a positive signal should be
480	analyzed with respect to the following three contributory elements: (a) co-
481	existence of maternal toxicity, (b) presence of a dose-response
482	relationship, and (c) the observation of rare events.
483	

<div align="center">

Maternal Toxicity

</div>

484	
485	
486	In weighing a signal of toxicity, the magnitude of adverse effects in
487	the offspring versus the severity of maternal (and, for fertility studies,
488	paternal) toxicity should be considered when drawing a conclusion
489	about the relevance of the F_0 toxicity to effects observed in the
490	offspring. This assessment is relevant to all seven classes of
491	reproductive and developmental toxicity. A positive signal occurring

492 at doses that are not maternally toxic increases concern for human
493 reproductive or developmental toxicity. If a positive signal is
494 observed only in the presence of frank maternal toxicity, there is
495 decreased concern, provided that the positive signal may be reasonably
496 attributed to maternal toxicity.[6]
497
498 When evaluating a positive signal in two or more species,
499 assessment of the implications of maternal or paternal toxicity
500 should be based on a composite analysis of the data from all
501 adequately studied species. If a positive signal is seen in two
502 or more species in the absence of maternal toxicity, there is
503 increased concern for adverse human reproductive outcomes.
504 If a positive signal is seen only in the presence of clear relevant
505 maternal toxicity in multiple species, there is decreased
506 concern.   If there is nonconcordance between test species as to
507 the presence and relevance of maternal toxicity, there may be
508 no change in the overall level of concern for this contributory
509 element.
510
511 If any species is considered inappropriate to assessing the
512 implications of maternal or paternal toxicity, the evaluation
513 should be performed using the remaining available data.
514
515 **Dose-Response Relationship**
516
517 Concern for human reproductive or developmental toxicity is
518 increased when a positive signal is characterized by any of the
519 following: (1) increased severity of adverse effects with an
520 increase in dose, (2) increased incidence of adverse effects with
521 an increase in dose, or (3) a high incidence of adverse effects
522 across all dosed groups. Conversely, the absence of all three of
523 these indicia of dose-response would be cause for unchanged
524 or decreased concern.
525
526 If multiple species are evaluated, a clear dose response across
527 all tested species increases concern. If a positive signal occurs
528 in more than one species, only one of which demonstrates one
529 of the dose-response relationships described above, the level of
530 concern will generally be unchanged. If there is no dose-
531 response in any species, there is decreased concern for this
532 contributory element.
533
534 **Rare Events**
535

---

[6] The attribution of adverse fetal effects to maternal (or paternal) toxicity can be based on previously collected data demonstrating the relationship between the maternal/paternal and reproductive effects.

536	Developmental toxicity studies usually lack the statistical power to
537	detect subtle increases in rare events. Thus, an increased frequency of
538	positive signals for rare events in drug-exposed animals increases
539	concern for reproductive or developmental toxicity in humans. The
540	absence of an increased frequency of rare events, however, does not
541	decrease concern.
542	
543	When multiple species (more than two) are studied, an increased
544	frequency of positive signals for rare events in more than one species
545	increases concern for adverse outcomes in humans even if not all
546	species have an increased frequency of positive signals.
547	
548	c. Pharmacodynamics
549	
550	A positive signal should be analyzed with respect to the following
551	three pharmacodynamic elements: (a) the therapeutic index, (b)
552	biomarkers as a benchmark, and (c) the similarity between the
553	pharmacologic and toxicologic mechanisms.
554	
555	**Therapeutic Index (TI)**
556	
557	The TI is used to identify the extent to which there is overlap
558	between therapeutic doses and doses that cause reproductive or
559	developmental toxicity. It is unusual to obtain well-defined dose-
560	response curves for toxicity and efficacy from a single species.
561	Thus, the use of estimations or surrogate endpoints (related to the
562	therapeutic mechanism) for this evaluation may be warranted. To
563	reduce the impact of variation in the slope of the dose-response
564	curves, estimation of the TI should generally be based on
565	comparison of the TD_{10} and the ED_{90} concentrations.[7]
566	
567	If the $TI_{10/90}$ is < 5, there is increased concern for reproductive or
568	developmental toxicity in humans, as there is limited separation in the
569	doses causing adverse effects from those responsible for efficacy. If
570	the $TI_{10/90}$ ratio falls between 5 and 20, the level of concern is
571	unchanged. If the $TI_{10/90}$ ratio is > 20, there is decreased concern

---

[7] The TD_{10} (toxic dose or concentration) should be defined by the C_{max} (or other appropriate exposure metric) that produced the toxic reproductive or developmental response in 10% of a *responsive* or *sensitive* species, whereas the ED_{90} (efficacious dose or concentration) should be defined by the C_{max} (or other appropriate exposure metric) that produced the desired effect in 90% of the test species. These parameters can be estimated. Preferably, both the TD_{10} and ED_{90} would be defined in the same species. In some instances estimation of the ED_{90} can be based on in vitro cell inhibition studies (frequently seen for antibiotics and antineoplastic agents). Although less desirable, efficacy data can be derived from another species, but caution should be exercised in such situations. The same exposure metric should be used in the estimation of the TD_{10} and ED_{90} values. Scientific justification for the drug exposure metrics used for comparison should be provided.

572	because of the wide separation in doses causing adverse effects from
573	those resulting in efficacy.
574	
575	If there are data available to determine the $TI_{10/90}$ ratio in multiple
576	species, assessment of the level of concern for this element should
577	be based on an integrated analysis of data from all adequately
578	studied species. The extent of concordance in the size of the $TI_{10/90}$
579	between species may increase, decrease, or leave unchanged the
580	level of concern (i.e., the greater the concordance, the more likely
581	concern will be increased). In the event of nonconcordance of the
582	TI ratios between multiple test species, the nature of the positive
583	signals observed and the relevance of the endpoint and test species
584	to the human condition should be considered before making an
585	assessment. In the event that one species is considered
586	inappropriate to the analysis, the evaluation should be performed
587	without reference to that species.
588	
589	**Biomarkers as a Benchmark**
590	
591	There may be circumstances in which an effect on a biomarker is
592	consistently seen in multiple species at doses lower than the NOEL for
593	demonstrable reproductive/developmental toxicity. If there is an effect
594	on this biomarker at or below the therapeutic dose in humans, there is
595	increased concern for reproductive or developmental toxicity in
596	humans. If this biomarker is responsive to the drug in humans, can be
597	monitored, and is not affected at the therapeutic dose, there may be
598	decreased concern.
599	
600	**Similarity between Pharmacologic and**
601	**Reproductive Developmental Toxicologic Mechanisms**
602	
603	If a positive signal is an extension of, progression of, or related
604	response to the intended pharmacologic effect of the drug (e.g., delay
605	of parturition by drugs known to suppress uterine smooth muscle
606	contractility or hypotension in the offspring of dams treated during late
607	gestation with a drug known to lower blood pressure), there is
608	increased concern for reproductive or developmental toxicity in
609	humans. There is less concern if the positive signal is attributed to an
610	animal-specific pharmacological response, even though it may be an
611	extension of the pharmacologic effect of the drug (e.g., pregnancy loss
612	in rats due to hypo-prolactinemia).
613	
614	d. Concordance between the Test Species and Humans
615	

616	Concordance between the test species and humans should be evaluated
617	with respect to: (a) the metabolic and drug distribution profiles, and (b)
618	the general toxicity profiles, and (c) biomarker profiles.
619	

Metabolic and Drug Distribution Profiles

622	Drug distribution, elimination, and biotransformation (pathways and
623	metabolites) in the test species and in humans should be compared.
624	Quantitative differences in metabolic/drug distribution profiles
625	between the test species and humans are often seen, and may not have
626	important implications and should not be overemphasized.
627	Reproductive and developmental toxicities induced by compounds
628	whose metabolic and distribution profiles are very similar in animals
629	and humans increases concern for reproductive or developmental
630	toxicity in humans. For compounds with highly dissimilar metabolic
631	or tissue distribution profiles in animals and humans, there is less
632	concern if the toxic effect seen in the test species can be attributed to a
633	metabolite or tissue distribution profile not seen in humans. For any
634	other scenario, concern is unchanged.
635	
636	When there are significant differences in drug distribution or metabolic
637	profiles between several species, yet each test species demonstrates a
638	positive signal for a reproductive or developmental toxicity, the toxicity is
639	assumed to be attributable to the parent drug or a common bio-
640	transformed product and concern is increased.

General Toxicity Profiles

644	If the overall toxicity profile of a drug in one or more test species with
645	a positive signal is similar to that in humans, there is increased concern
646	for reproductive or developmental toxicity in humans. If the overall
647	toxicity profiles are dissimilar, there may be decreased concern. When
648	general toxicology data are available for more than one species, the
649	determination of the level of concern (increased, decreased, or
650	unchanged) should be based on an assessment of each test species'
651	ability to indicate human adverse effects in response to the drug.

Biomarker Profiles

655	When biomarker profiles are available for comparison, an approach
656	similar to that described in the assessment of General Toxicity Profiles
657	(previous section) may be useful.
658	
659	e. Relative Exposures
660	

661   When considering the relative exposure comparisons discussed below,
662   more emphasis should be placed on a parameter within this factor
663   when there is a scientifically plausible link between the exposure
664   metric (or biomarker) and the adverse reproductive (or developmental)
665   effect.

666

667   **Kinetic Comparison of Relative Exposure**

668

669   Comparison of systemic drug exposure at the NOEL for the
670   reproductive or toxicity class in the test species to that in humans at
671   the maximum recommended dose is a critical determination. This
672   comparison should be based on the most relevant metric (e.g., AUC,
673   C_{max}, C_{min}, BSA [body surface area] adjusted dose). In general, there
674   is increased concern for reproductive or developmental toxicity in
675   humans for relative exposure ratios (animal:human) that are ≤ 10,
676   decreased concern for exposure ratios ≥ 25, and no change in concern
677   for ratios between 10 and 25. When applicable, the relative exposure
678   ratio should consider both the parent compound and its metabolites.
679   For example, it is appropriate to combine parent and metabolite when
680   both are pharmacologically active and the activity relates to the
681   reproductive or developmental toxicity.

682

683   Where there are exposure data for multiple test species, the NOEL
684   exposure for each should be compared to human exposure at the
685   maximum recommended dose. If the exposure ratios are low (≤ 10 fold) in
686   multiple species with a positive signal, there is increased concern. If the
687   exposure ratios are high (≥ 25 fold), there is decreased concern. In the
688   event a significant difference in relative exposures is observed between
689   multiple test species, the appropriateness of the metric (for example, AUC,
690   C_{max}) being used to define the inter-species exposure comparisons should
691   be re-assessed. If an alternative metric fails to reduce the disparity
692   between species, the assessment of concern should be based on the lowest
693   ratio (i.e., in the most sensitive species).

694

695   Relative interspecies exposure data should be evaluated in light of species
696   differences in protein binding (free drug concentration), receptor affinity
697   (if related to the positive signal) or site specific drug concentrations. In the
698   absence of meaningful differences between the test species and humans in
699   these parameters, the interspecies comparisons should be based on total
700   drug exposure.

701

702   **Biomarkers as a Measure of Relative Exposure**

703

704   The purpose of this relative exposure metric is to compare the dose
705   causing a reproductive toxic effect in the test species to the
706   therapeutic dose in humans, normalized to the doses causing a

707	response common to both species. In practice, this is done by
708	taking the NOEL for the adverse reproductive or developmental
709	effect and dividing by the dose at which the biomarker response is
710	seen in the test species. This is compared to the human therapeutic
711	dose divided by the dose at which the biomarker response is seen
712	in the human. The ratio calculated for animals is then divided by
713	the ratio calculated for humans. When this ratio of relative
714	biomarker exposure (animal:human) is ≤ 10, there is increased
715	concern for human reproductive or developmental toxicity. When
716	this ratio is ≥ 25, there is less concern. When this ratio falls
717	between 10 and 25, the level of concern is unchanged.
718	
719	Where there are data to compute relative biomarker exposure ratios
720	for multiple species, the level of concern assessment should be
721	based on an integrated analysis of data from all adequately studied
722	species. Where there are nonconcordant biomarker ratios between
723	multiple test species, the relevance of the biomarker as expressed
724	in the various species should be considered before making an
725	assessment. If there is no scientific rationale for the disparity
726	between species, the biomarker, as a measure of exposure, will be
727	of questionable utility.
728	
729	f. Class Alerts
730	
731	Consideration of a *class associated effect* should be based on prior human
732	experience for a drug with related chemical structure (parent or
733	metabolite) or related pharmacologic effect, and with known reproductive
734	or developmental outcomes in humans. There is increased concern for
735	reproductive or developmental toxicity in humans when the drug is from a
736	class of compounds known to produce adverse effects in the same toxicity
737	class in humans and animals. There is decreased concern only in
738	circumstances in which a class of compounds, although demonstrating
739	adverse effects in animals, has been previously shown to have no related
740	adverse effects on human reproduction or development. In the absence of
741	adequate human reproduction or developmental data for a class, the level
742	of concern is unchanged.
743	
744	g. Summary/Integration of Positive Findings
745	
746	Notes on the use of the Integration Tool (see Figure C end of
747	document):
748	
749	The factors discussed below are derived from a limited sample of
750	pharmaceuticals where the clinical outcomes are reasonably well
751	defined. CDER believes that using specific factors and benchmark
752	values to assess the potential to increase risk to humans for adverse

753	reproductive and developmental outcomes will result in a more
754	unbiased and uniform evaluation. CDER also believes this approach
755	will help identify specific areas of additional information about a
756	pharmaceutical that would be useful in more fully defining risk and
757	allow specific analysis of areas of disagreement that influence the risk
758	evaluation.
759	

760   1.   Where there is a positive finding in nonclinical or general
761   toxicology studies for one of the seven classes of reproductive or
762   developmental toxicity, there is a potential for increased human
763   risk. In evaluating the level of increased risk, positive findings
764   from each of the seven classes of reproductive and developmental
765   toxicity should be assessed separately. All relevant information
766   should be considered.

768   2.   In evaluating the level of concern for each of the six factors in the
769   overall assessment, the analysis should reflect the weight of
770   evidence taking into account the quality and type of data under
771   consideration for each factor (i.e., should not be merely an
772   arithmetic summation of the contributory elements for each factor).
773   For each factor there should be a determination of increased (+1),
774   decreased (-1), or no change (0) in the level of concern.

776   3.   The values for the six factors should then be summed to arrive at
777   one of the following overall conclusions for each class of
778   reproductive or developmental toxicity: (1) the drug is predicted to
779   increase risk, (2) the drug may increase risk, or (3) the drug does
780   not appear to increase risk of that class of reproductive or
781   developmental toxicity in humans. Where there is sufficient
782   information about the drug to assess each of the six factors within
783   Figure C, a net value of $\geq +3$ suggests a drug is predicted to
784   increase risk for that class of toxicity in humans, a value between
785   +2 and –2 suggests that the drug may increase the risk, and a value
786         $\leq$ -3 suggests the drug does not appear to increase the risk.

789   The summary risk conclusions for the outcomes of analyses using
790   Figure "C" are:

792   **Does Not Appear to Increase Risk**: The drug is not anticipated to
793   increase the incidence of adverse reproductive (or developmental) effects
794   above the background incidence discussed in humans when used in
795   accordance with dosing information in the product label.

797   **May Increase Risk**: The drug may increase the incidence of adverse
798   reproductive (or developmental) events above the background incidence in

799   humans when used in accordance with the dosing information in the
800   product label.
801
802   **Predicted to Increase Risk**: The drug is expected to increase the
803   incidence of adverse reproductive (or developmental) events above the
804   background incidence in humans when used in accordance with the dosing
805   information in the product label.
806

807
808   **GLOSSARY**
809
810 **ADME** − absorption, distribution, metabolism, and elimination
811
812 **Biomarker** − a clinical or laboratory parameter that is known, or thought, to correlate
813 with a toxicity outcome or with exposure
814
815 **Class Alert** – an adverse reproductive or developmental effect previously demonstrated
816 in humans by closely related chemical entities or compounds with similar
817 pharmacodynamic effects
818
819 **Contributory Elements** − specific items of information that contribute to the overall
820 evaluation and conclusion for each factor of Figure C
821
822 **Developmental Toxicity** − any adverse effect induced prior to attainment of adult life. It
823 includes effects induced or manifested in the embryonic or fetal period and those induced
824 or manifested postnatally. These are generally adverse effects that affect the F_1
825 generation and are divided into four endpoints, mortality, dysmorphogenesis, alterations
826 to growth, and functional toxicities.
827
828 **Factor** – for purposes of this guidance, a factor is one of the six components used to
829 evaluate the level of concern for a positive signal in a class of developmental or
830 reproductive toxicity to determine whether there is an increase (assigned value of +1), a
831 decrease (-1), or no change (0) in the overall concern for that class of toxicity. There are
832 six factors: (1) signal strength, part I; (2) signal strength, part 2; (3) pharmacodynamics;
833 (4) concordance between the test species and humans; (5) relative exposures; and (6)
834 class alerts. They are all portions of the Integration Tool (Figure C) and are discussed in
835 Section 4.
836
837 **Fertility** – reproductive competence
838
839 **Lactation** − the secretion of milk or the period of milk secretion
840
841 **Malformation** − a permanent alteration (anomaly) in which there is a morphologic defect
842 of an organ or a larger region of the body, resulting from an abnormal developmental
843 process. They generally occur at a low frequency in the control population and/or will
844 adversely affect survival, growth, or development of functional competence.
845
846 **Maternal (Paternal) Toxicity** – toxicity to the mother (maternal) or the father (paternal)
847 in a reproductive toxicology study, but not necessarily a toxicity to reproductive function
848
849 **Parturition** – labor and delivery
850
851 **Positive Signal** − a treatment related reproductive or developmental toxicity
852

853 **Rare Event** – an endpoint that occurs in less than 1 percent of the control animals in a
854 study and in historical control animals
855
856 **Reproductive Toxicity** – structural and/or functional alterations that may affect
857 reproductive competence of the F_0 generation. These are divided into three classes—
858 fertility, parturition, and lactation.
859
860 **Therapeutic Index** – for the purpose of this document, the ratio of the dose that induces
861 a toxicologic effect in approximately 10 percent of the treated animals (TD_{10}) compared
862 to the dose that brings about the intended result of the therapeutic in 90 percent of the
863 treated animals (ED_{90})
864
865 **Toxicologic Effect** – any adverse effect of a therapeutic
866
867 **Variation** - an alteration that may occur at a relatively high frequency and/or represents a
868 retardation in development, a transitory alteration, or a permanent alteration not believed
869 to adversely affect survival, growth, development, or functional competence.
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891 **APPENDIX A**
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893
894 **SAMPLE SCENARIOS AND RISK CONCLUSIONS FOR SITUATIONS IN**
895 **WHICH THERE ARE NO POSITIVE FINDINGS FOR A CLASS OF**
896 **REPRODUCTIVE OR DEVELOPMENTAL TOXICITY**
897 **(ASSESSMENTS USING FIGURE B)**
898
899
900 *Case 1*. The animal species and dose selections were considered appropriate, there
901 is no class alert for the drug, and no positive signals were observed for any class
902 of developmental toxicity.
903
904 *Summary Risk Conclusion 1*. Based on studies in animals, there does not appear
905 to be an increased risk for adverse developmental effects in humans.
906
907 *Case 2*. No positive signals were observed for any class of reproductive toxicity
908 and there are no human data for the drug. However, other drugs in the same
909 pharmacologic class have demonstrated adverse reproductive effects in humans
910 (i.e., a class alert).
911
912 *Summary Risk Conclusion 2*. The risk for adverse reproductive effects in humans
913 is unknown. Although no effects were observed in adequately conducted
914 reproductive toxicity studies in animals, and there is no information about adverse
915 reproductive effects of the drug in humans, adverse reproductive effects have
916 been observed in humans with related drugs. (should specify the type of adverse
917 effects observed in humans with other members of the class and the basis for the
918 class designation—e.g., chemically or pharmacologically related).
919
920 *Case 3*. The available developmental toxicity studies are considered to lack
921 predictive value because exposures to the drug in animal studies conducted at the
922 MTD were not considered adequate when compared to the maximum exposure in
923 humans.
924
925 *Summary Risk Conclusion 3*. The risk for adverse developmental effects in
926 humans is unknown. Although there were no observed adverse developmental
927 effects in adequately conducted toxicity studies in animals, exposures achieved in
928 the animal studies may not have been adequate to fully evaluate the potential for
929 the drug to increase the risk of reproductive or developmental toxicity in humans.
930
931 *Case 4*. The animal models were not considered adequate to test the drug because
932 the test species in the reproductive toxicity studies lacked the cellular receptor
933 responsible for the pharmacologic activity of the drug in humans, or did not
934 demonstrate a toxicity or metabolite profile similar to that in humans.
935
936

937   *Summary Risk Conclusion 4*. The risk for adverse reproductive effects in humans
938   is unknown. Although there were no observed adverse effects in animal
939   reproductive toxicity studies, there remains some concern for increased risk of
940   adverse reproductive effects in humans exposed to the drug because the test
941   species may not be predictive of the human condition.
942
943   *Case 5*. In animal studies considered appropriate for predicting the human
944   response, and at exposure levels significantly greater than expected in humans,
945   there was a positive signal in one class of developmental toxicity and no observed
946   adverse effects in a related class of developmental toxicity. The positive signal
947   was evaluated using Figure C and it was concluded that the drug may increase the
948   risk of that class of toxicity in humans.
949
950   *Summary Risk Conclusion 5*. Based on studies in animals, the drug may increase
951   the risk of [the class of developmental toxicity in which toxicity was observed] in
952   humans. Although no findings were observed for [type of developmental toxicity
953   in same category] there may be some relationship between the incidence of [the
954   class of toxicity in which toxicity was observed] and [the related class of toxicity
955   not observed].
956
957

FIGURE A. OVERALL DECISION TREE FOR EVALUATION OF REPRODUCTIVE/DEVELOPMENTAL TOXICITIES

1. AVAILABILITY OF STUDIES? — NO → "**UNKNOWN**" OR "NOT EVALUABLE" RISK

INFORMATION IS NOT AVAILABLE TO ASSESS RISK

YES ↓

2. RELEVANCE OF STUDIES (TEST SYSTEM AND ROUTE) — NO → "**UNKNOWN**" OR "NOT EVALUABLE" RISK

DEFINE NON-RELEVANCE OF TEST SYSTEM OR STUDY

(DO NOT USE FIGURE C)

YES ↓

3. PRESENCE OF A SIGNAL FOR AN ENDPOINT? — NO → **"NO OBSERVED EFFECT"**

USE FIGURE B FOR INTEGRATION OF DATA FOR ENDPOINTS WITH NO SIGNAL

YES ↓

"POSITIVE EFFECT OBSERVED"
USE FIGURE C FOR INTEGRATION OF DATA
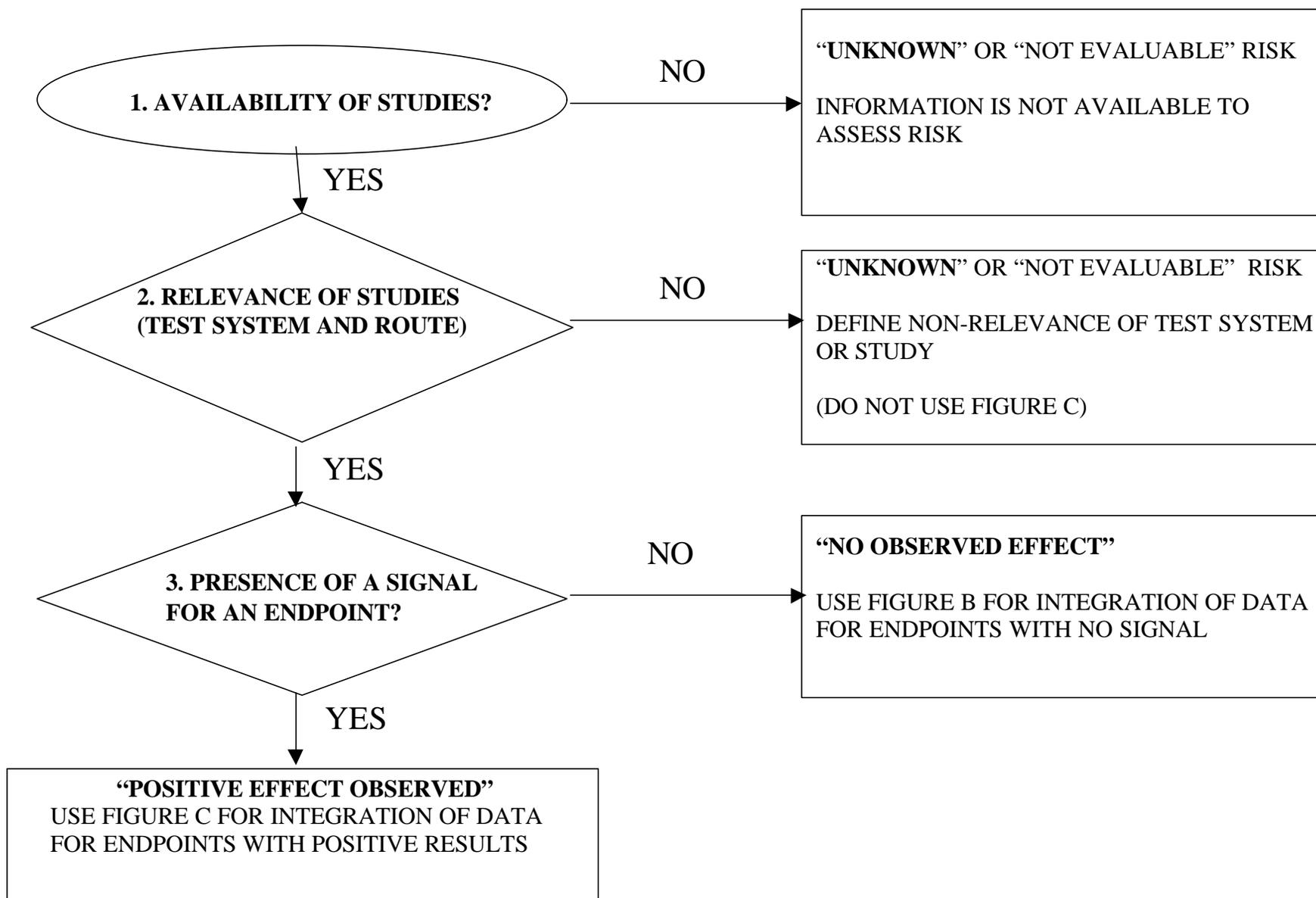FOR ENDPOINTS WITH POSITIVE RESULTS

24

FIGURE B. DECISION TREE FOR REPRODUCTIVE/DEVELOPMENTAL TOXICITIES WITH NO SIGNAL
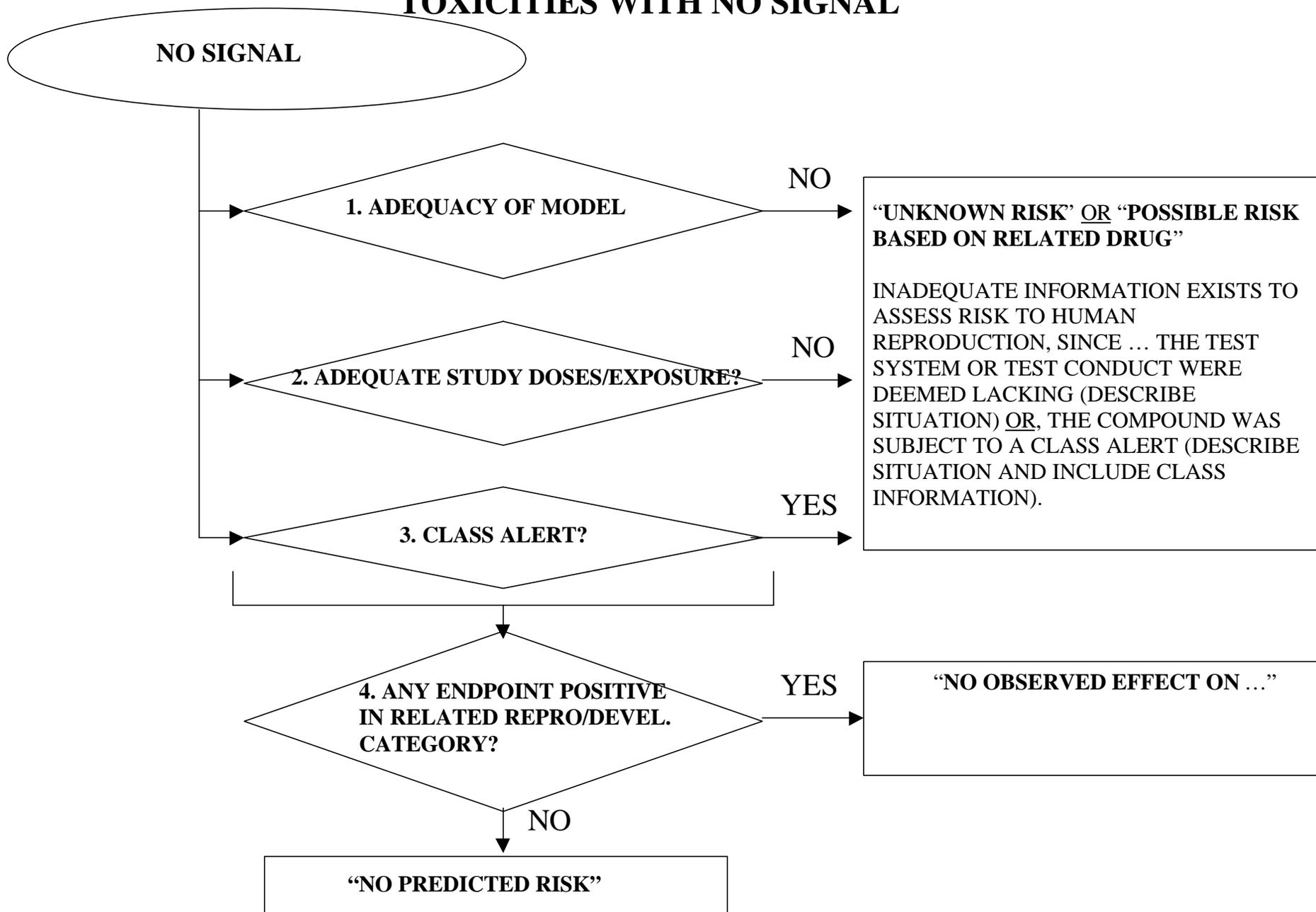
FIGURE C - INTEGRATION TOOL FOR REPRODUCTIVE OR DEVELOPMENTAL TOXICITIES WITH A POSITIVE SIGNAL

CLASSES OF TOXICITY OR SIGNALS

REPRODUCTIVE TOXICITY
1. Fertility
2. Parturition
3. Lactation

DEVELOPMENTAL TOXICITY
1. Mortality
2. Dysmorphogenesis
3. Alterations to growth
4. Functional toxicity

POSITIVE SIGNAL

SIGNAL STRENGTH I

SIGNAL STRENGTH II

PD

ADME TOX

EXPO-SURE

CLASS, ALERTS

PROGRESS TO NEXT STEP

HUMAN DATA

PREDICTED TO INCREASE HUMAN REPRO. RISK

Concern increasing

MAY INCREASE HUMAN REPRO. RISK

DOES NOT APPEAR TO INCREASE HUMAN REPRO. RISK

Concern Decreasing

HUMAN DATA

DATA INTEGRATION PROCESS

ANIMAL DATA → **HUMAN DATA**

26