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Overview of comments received on Addendum to the ICH guideline S1B on testing for carcinogenicity of pharmaceuticals (EMA/CHMP/ICH/272147/2021)

Please note that comments will be sent to the ICH **S1B** EWG for consideration in the context of Step 2b of the ICH process.

1. General comments – overview

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
European Coalition to End Animal Experiments (ECEAE)	0	0		We thank you very much for the draft addendum and the concept of waiving two-year carcinogenicity studies in rats in certain cases. It is certainly also your goal to reduce animal testing as far as possible. As a supplement, we would kindly ask you to consider the statements of Corton et al. 2020 as well as Hill et al. (2020) (references below) as far as possible in your strategy, especially for example case 3, in which an existing or absent risk of carcinogenicity cannot be assessed. Rationale: In their publications, the investigators report that measurement of the six most common initial molecular events (MIEs) in liver cancer AOPs already in the legally required short-term tests is sufficient to assess a probable tumorigenic potential in the liver (1). Five biomarkers under consideration for this purpose are composed of those for genotoxicity, the cytotoxicity, as well as for the activation of one or more xenobiotic receptors (aryl hydrocarbon receptor (AhR), constitutively activated receptor (CAR), estrogen receptor (ER), and peroxisome proliferator-activated receptor α (PPARα)) (2). This new design was also discussed amongst others during the recent World Congress on Alternatives to Animal Testing in the Life Sciences early last month.	
EFPIA	0	0		General Comment: EFPIA is highly supportive of the increased flexibility the addendum provides by allowing, in certain cases, a weigh-of-evidence approach that does not involve the conduct of a 2-year rat carcinogenicity study. EFPIA is also supportive of the use of comparative exposures (ie 50-fold margin) as a valid principle for high-dose selection in 6-months rasH2 Tg mouse studies. The following comments are relatively minor and are submitted for consideration by the Expert Working Group.	

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European Coalition to End Animal Experiments (ECEAE)	0	0		We thank you very much for the draft addendum and the concept of waiving two-year carcinogenicity studies in rats in certain cases. It is certainly also your goal to reduce animal testing as far as possible. As a supplement, we would kindly ask you to consider the statements of Corton et al. 2020 as well as Hill et al. (2020) (references below) as far as possible in your strategy, especially for example case 3, in which an existing or absent risk of carcinogenicity cannot be assessed. Rationale: In their publications, the investigators report that measurement of the six most common initial molecular events (MIEs) in liver cancer AOPs already in the legally required short-term tests is sufficient to assess a probable tumorigenic potential in the liver (1). Five biomarkers under consideration for this purpose are composed of those for genotoxicity, the cytotoxicity, as well as for the activation of one or more xenobiotic receptors (aryl hydrocarbon receptor (AhR), constitutively activated receptor (CAR), estrogen receptor (ER), and peroxisome proliferator-activated receptor α (PPARα)) (2). This new design was also discussed amongst others during the recent World Congress on Alternatives to Animal Testing in the Life Sciences early last month. (1) Corton JC, Hill T, Sutherland JJ, Stevens JL, Rooney J. A Set of Six Gene Expression Biomarkers Identify Rat Liver Tumorigens in Short-term Assays. Toxicol Sci. 2020 Sep 1;177(1):11-26. doi: 10.1093/toxsci/kfaa101. PMID: 32603430; PMCID: PMC8026143. (2) Hill T, Rooney J, Abedini J, El-Masri H, Wood CE, Corton JC. Gene Expression Thresholds Derived From Short-term Exposures Identify Rat Liver Tumorigens. Toxicol Sci. 2020 Sep 1;177(1):41-59. doi: 10.1093/toxsci/kfaa102. PMID: 32603419; PMCID: PMC7990321.	
International Council on Animal Protection in Pharmaceutical Programs (ICAPPP)	0	0		ICAPPP welcomes the publication of specific weight-of-evidence (WoE) criteria that can be used to waive the two-year rat bioassay in certain situations, which will subsequently lead to a reduction in the use of rats for carcinogenicity testing. We also support the ICH in their encouragement of an integrative approach to reduce the use of animals in accordance with the 3Rs (reduce/refine/replace), and to shift resources onto generating more mechanistic-based carcinogenicity assessments. However, considering the highly disputed relevance of rodent cancer bioassays in their utility to predict carcinogenicity risk in humans, we request the ICH to consider the following comments and recommended revisions: 1. Publication of a revision to the guideline rather than an Addendum, 2. Full harmonization across all ICH regions, 3. Eliminate the recommendation of mouse studies regardless of WoE assessment, and 4. Clearly recommended non-animal approaches to be considered in the main WoE approach.	
International Council on Animal Protection in Pharmaceutical Programs (ICAPPP)	0	0		**1. Publication of a revision to the guideline rather than an Addendum** We request that the ICH update or replace the 1997 ICH S1B guideline on 'testing for carcinogenicity of pharmaceuticals' instead of publishing an 'Addendum' to be read in conjunction with the original guideline. It is not uncommon for the ICH to replace outdated ICH guidelines with newer versions, for example, the ICH S5(R3) guideline was not published as an addendum but as a replacement to the original S5 guideline. The ICH S1B guideline outlines a 'basic scheme' of testing that strongly recommends the conduct of a two-year rat study in all scenarios along with a short/medium term or long-term mouse study. The two-year rat study is the favored test method for carcinogenicity assessment in the original guideline as it highlights some of the limitations to the mouse studies, including "the high susceptibility of mouse liver to nongenotoxic chemicals has been the subject of many symposia and workshops. These have concluded that these tumours may not always have relevance to carcinogenic risk in humans and can potentially be misleading". The original guideline is now in contradiction to the new WoE-based approach set out in the draft addendum. Therefore, to avoid confusion and to ensure that the new WoE approach is adequately utilized and implemented, we request the ICH to replace the outdated S1B guideline with a WoE-based S1(R1) guideline rather than publish the Addendum as a separate, optional document.	

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International Council on Animal Protection in Pharmaceutical Programs (ICAPPP)	0	0		**2. Reach full harmonization across all ICH regions** The purpose of ICH guidelines is to present harmonized testing requirements that are accepted across all ICH regions to avoid duplicative testing that is not health protective. We therefore request that Japan and the United States (US) align with the EU in their recommendations for carcinogenicity testing. The EU has agreed that if the WoE assessment determines that a two-year rat bioassay would not add value to completing a human carcinogenicity risk assessment, then neither would a mouse study (of any type or duration). This contrasts with the recommendation laid out in the draft addendum, which states that a mouse carcinogenicity test remains "a recommended component of a carcinogenicity assessment plan" even in cases where the WoE assessment indicates that a rat study would not add value. We strongly support the EU's position not to recommend any rodent carcinogenicity studies when the WoE evaluation indicates that they would add no value and urge the ICH to seek harmonization from the US and Japan.	
International Council on Animal Protection in Pharmaceutical Programs (ICAPPP)	0	0		**3. Remove recommendation of mouse studies regardless of WoE** As previously noted, the ICH S1B guideline states "the highly susceptibility of mouse liver to nongenotoxic chemicals has been the subject of many symposia and workshops. These have concluded that these tumors may not always have relevance to carcinogenic risk in humans and can potentially be misleading", thus demonstrating a pre-existing acknowledgment of the limitations of the mouse carcinogenicity studies in providing a health protective hazard and risk assessment. There is substantial evidence to demonstrate that rodent cancer bioassays inaccurately predict carcinogenicity potential in humans, including poor reproducibility and a high false-positive rate, dosing that is not metabolically relevant, and modes of action that are not biologically relevant to humans (refs 1-13). These limitations have been noted for both the rat and the mouse cancer bioassays. For example, a notable study from Osimitz et al. evaluated 710 non-genotoxic substances, including pharmaceuticals, reported "A careful analysis showed that their carcinogenicity in mice is irrelevant for assessment of human cancer hazards" and "As a result, we propose that the inclusion of the mouse bioassay in the standard assessment scheme for non-genotoxic chemicals is no longer necessary" (ref 10). The wording of section 2.3 of the draft addendum is confusing as it encourages a mouse carcinogenicity study (2-year or short-term transgenic) to be conducted in all circumstances; however, the reported WoE case rationales in the draft addendum clearly demonstrate no carcinogenic potential in humans (i.e., cases 1 and 4). These cases demonstrate the carcinogenic potential to humans can be determined without a mouse carcinogenicity test, so the conduct of the mouse test(s) will not provide human relevant information to support a health protective WoE safety assessment.	

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International Council on Animal Protection in Pharmaceutical Programs (ICAPPP)	0	0		**3. Remove recommendation of mouse studies regardless of WoE - continuation** Further, there are also concerns that the overall 3Rs benefits of the new recommended approach will be offset by a significant increase in the use of transgenic mice. According to a recent ECVAM/ESTIV workshop, "the introduction of specific shorter-term carcinogenicity studies, as the transgenic mouse model, seemed at first to impact positively on the 3Rs, showing promises for more technical specificity and impact on animal number. However, the transgenic model has resulted not to be a real reduction model because of the amount of animals needed for the breeding of the specific knockouts" (ref 7). In particular, rasH2-Tg mice are maintained as hemizygotes for the transgene; therefore, twice the number of mice needed for short-term studies are produced when wild-type littermates are counted, eliminating the apparent reduction benefit. We request the ICH to remove its recommendation that mouse studies should remain a main component of carcinogenicity testing, regardless of WoE factors. Waivers for mouse carcinogenicity studies should be recommended in all cases where the WoE evaluation indicates that a rat carcinogenicity study would not add value – this would guarantee a reduction in the use of animals for carcinogenicity testing and would also result in full harmonization with the EU. Furthermore, in cases where the WoE assessment leads to a conclusion of uncertainty regarding human carcinogenicity potential, and a rodent study is required, we urge the ICH to recommend the conduct of only one study i.e. either a 2-year rat or a mouse carcinogenicity study (2-year or short-term transgenic), depending on which is likely to add the most value to the risk assessment.	
International Council on Animal Protection in Pharmaceutical Programs (ICAPPP)	0	0		**4. Addition of non-animal approaches to the main WoE approach** While the use of alternative in vitro test systems, read-across, and data from emerging technologies are mentioned in the draft addendum, we recommend specific language be added to clarify the use of non-animal approaches to be considered in the main WoE section. For example, non-animal methods could include, the use of cell transformation assays (CTA) using Syrian hamster embryo cells (SHE) and the BALB/c 3T3 mouse fibroblast cell line. These assays have been recommended by the European Centre for the Validation of Alternative Methods (ECVAM) and endorsed by EURL ECVA Scientific Advisory Committee (ESAC) for their use in carcinogenicity testing through an integrated testing strategy and have been shown to be a useful tool to identify both genotoxic and nongenotoxic carcinogens with an estimated 90-95% sensitivity. Another useful tool that should be suggested for consideration in the WoE approach is the use of QSAR's, which, in combination with other assays in integrated testing strategies, are valuable to support carcinogenicity assessment. More recently, data-rich "omics" technologies are being investigated for their potential to generate whole genome expression profiles that could be used to evaluate chemical carcinogens (ref 14). While this technology has to yet to be fully developed and validated, it could be mentioned as an example of an 'emerging technology' that has the potential to enhance human carcinogenicity risk assessment in the future. We urge the ICH to recommend the use of these non-animal approaches as part of the main WoE approach. The use of these approaches will strengthen the predictivity and relevance of the human risk assessment and lead to a lower incidence of cases where the carcinogenic potential of a substance is deemed "uncertain". This will provide a further reduction in the use of animals in the short term and could help encourage a paradigm shift away from rodent models entirely toward more human relevant non-animal models.	

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International Council on Animal Protection in Pharmaceutical Programs (ICAPPP)	0	0		References: 1. Alden, C.L. et al. (1996). A critical appraisal of the value of the mouse cancer bioassay in safety assessment. Toxicol Pathol 24, 722–725. https://doi.org/10.1177/019262339602400610 2. Alison, R.H. et al. (1994). Neoplastic lesions of questionable significance to humans. Toxicol Pathol 22, 179–186. https://doi.org/10.1177/019262339402200211 3. Bourcier, T. et al. (2015). Improving prediction of carcinogenicity to reduce, refine, and replace the use of experimental animals. J Am Assoc Lab Anim Sci 54, 163–169. 4. Cohen, S.M. (2017). The relevance of experimental carcinogenicity studies to human safety. Curr. Opin. Toxicol. 3, 6–11. https://doi.org/10.1016/j.cotox.2017.04.002 5. Cohen, S.M. (2004). Human carcinogenic risk evaluation: An alternative approach to the two-year rodent bioassay. Toxicol Sci 80, 225–229. https://doi.org/10.1093/toxsci/kfh159 6. Cohen, S.M et al. (2019). Chemical carcinogenicity revisited 3: Risk assessment of carcinogenic potential based on the current state of knowledge of carcinogenesis in humans. Regul Toxicol Pharmacol 103, 100–105. https://doi.org/10.1016/j.yrtph.2019.01.017 7. Corvi, R. et al. (2017). Moving forward in carcinogenicity assessment: Report of an EURL ECVAM/ESTIV workshop. Toxicol Vitr. 45, 278–286. https://doi.org/10.1016/j.tiv.2017.09.010 8. Goodman, J.I., 2018. Goodbye to the bioassay. Toxicol Res 7, 558–564. https://doi.org/10.1039/c8tx00004b 9. Luijten, M. et al. (2016). An integrative test strategy for cancer hazard identification. Crit. Rev. Toxicol. 46, 615–639. https://doi.org/10.3109/10408444.2016.1171294 10. Monro, A. (1996). Are lifespan rodent carcinogenicity studies defensible for pharmaceutical agents? Exp. Toxicol. Pathol. 48, 155–166. https://doi.org/10.1016/s0940-2993(96)80036-4 11. Osimitz et al. (2013). Evaluation of the utility of the lifetime mouse bioassay in the identification of cancer hazards for humans. Food Chem Toxicol 60, 550–562. https://doi.org/10.1016/j.fct.2013.08.020 12. Paules, R.S. et al. (2011). Moving forward in human cancer risk assessment. Env. Heal. Perspect 119, 739–743. https://doi.org/10.1289/ehp.1002735 13. Ward, J.M. (2007). The two-year rodent carcinogenesis bioassay — Will it survive? J. Toxicol. Pathol. 20, 13–19. https://doi.org/10.1293/tox.20.13 14. Yauk, C.L. et al. (2020). A cross-sector call to improve carcinogenicity risk assessment through use of genomic methodologies. Regul. Toxicol. Pharmacol. 110, 104526. https://doi.org/10.1016/j.yrtph.2019.104526	

2. Specific comments on text

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
EFPIA	35	37	1.1	The scope section refers to "all small molecule pharmaceuticals". Please consider including a definition of "small molecule". For example are peptides with less than 40 amino acids or RNA-based therapeutics such as ASOs and siRNA's covered in the scope of this guidance?	Include a definition and/or give examples
EFPIA	36	37	1.1	There is mention that this adendum should be used in conjuction with S1 guidelines. Additional clarity would be helpful.	Consider creating a decision tree or flow diagram of how this addendum intersects with each of the S1 Guidances.
EFPIA	39	39	1.2	Wording suggestion for clarity	Change "testing scheme" to "evaluation process"
EFPIA	42	43	1.2	Wording suggestion for clarity	Change “adds value in completing a human carcinogenicity risk assessment.” to “adds value to a human carcinogenicity risk assessment.”
EFPIA	52	52	1.3	Wording suggestion for clarity	Change “scheme” to “paradigm”
EFPIA	84	84	2	The terms "well recognized mechnisms" and "human irrelevant" or the like terms are used several times. Please elaborate on what is meant by this. In other words what are the criteria to be met to achieve the "terms".	Include which criteria thought of and/or give examples
EFPIA	95	95	2.1	Revise line that is written as "These factors include:"	Consider revising to "These factors include but are not limited to:"
EFPIA	107	110	2.1	Please clarify whether atrophy in endocrine and reproductive tissues is considered evidence of a potential carcinogenic risk or whether the signal is intended to be interpreted in the context of accompanying compensatory feedback mechanisms (i.e., hypertrophy/hyperplasia).	

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EFPIA	109	110	2.1	We suggest revising the text from "…and results from reproductive toxicology studies" to "… and **relevant** results from reproductive toxicology studies, **if available**." This is because based on ICH S5(R3), weights of endocrine or reproductive organs and microscopic examination of endocrine or reproductive organs are not required as standard endpoints in reproductive toxicity studies and are only recommended when there is cause for concern based on mode of action or data from previous studies.	Revise the text from "…and results from reproductive toxicology studies" to "… and relevant results from reproductive toxicology studies, if available."
EFPIA	145	149	2.2	Multiple EFPIA member companies expressed concern regarding the process for seeking alingment with the DRAs of each region and have requested that ICH provide a global harmonization process. An alternate approach is to simply remove reference to seeking individual regulatory input as other ICH guidances do not generally provide advice on how to seek regulatory feedback on development plans. EFPIA recognizes that region-specific details are not generally included in ICH guidelines; however, we wanted to share this feedback with the EWG.	
EFPIA	145	149	212	Cosnider inclusion of 1) a template for a WOE document to be used in seeking regulatory alignment and 2) a decision tree for determining if a WOE assessment is warranted,	
EFPIA	145	145	2.2	If retained, in line 145 the text uses the term "WoE concludes" and footnote 6 uses the term "WoE indicates". If a difference is indented please clarify. If the terms are interchangeable suggest keeping the language consistent.	Please specify
EFPIA	151	154	2.3	Text indicates a carcinogenicity study in mice is still recommended even when WoE indicates a 2 yr rat study would not provide significant value. Footnote 6 lays out in detail the rationale for why a mouse study is still appropriate but then appears to indicate the EU is an exception. Does this mean that in all regions except EU, whatever the WoE assessment, a mouse study is expected (when adequate exposures are achievable) as part of the carcinogenicity assessment plan ?	Request that EWG provide greater clarification on the need for mouse studies including providing the rationale for a different approach in the EU.
EFPIA	154	157	2.3	Please could you also clarify the need (or no need) for using an alternative species (e.g. hamster) when either adequate systemic exposures or relevant pharmacology cannot be achieved in mice	
EFPIA	155	155	2.3	Please clarify was is meant by "data indicate that only subtherapeutic, pharmacologically inactive drug exposures can be achieved in the mouse"... Is it e.g. due to toxicity finding(s) limiting the dose, or poor absorbtion?	Please clarify and give examples
EFPIA	167	169	3	Exposure ratio of 50-fold in rasH2: is the calculation recommeanded using unbound fractions , even when the unbound fraction is greater in rodents than in humans ? ICHS1C (note 8) states that in this case, the comparison with total plasma concentrations of the drug is appropriate, the use of unbound concentrations being limited to cases where unbound fraction is higher in humans vs animals.	Provide additional clarification regarding the use of unbround fractions.
EFPIA	230	231	Appendix 1 - Preamble	The text properly indicates that based on the RND study, the lack of evidence of immunomodulation is an attribute that may contribute to the WoE that the results from a 2-year rat study would not contribute value to human carcinogenicity risk assessement. It is however also recognized in the document that standard rat and mouse carcinogenicity studies are not reliable for identifying this specific human risk (lines 115 and 116). The rationale in Case 3 actually states that while immunomodulation was observed in monkeys, "it is not expected to be further informed by a rat carcinogenicity study".	Recommend a footnote to the statement on lines 230 - 231 to indicate that it does imply that a 2-year rat study is **neither** recommended nor needed based on the sole rationale that immunomodulation is associated with the drug.
EFPIA	267	268	app2	Could you clarify what a non-mammalian target is ?	Suggest including example to clarify such as "viral, bacterial"
EFPIA	415	415	Appendix 1 - Preamble	The word "Study" is underlined. (likely a typo)	Please correct typo.
EFPIA	423	423	app2	Could you clarify the sentence (..) not empirically addressed? Was this a test-article effect but the mechanism of the change had not been defined?	

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International Council on Animal Protection in Pharmaceutical Programs (ICAPPP)	60	63	2	Current text: "In cases where the WoE assessment leads to a conclusion of uncertainty regarding human carcinogenicity potential, the approach described in S1B of conducting a 2-year rat carcinogenicity study together with a carcinogenicity assessment in mice (short term or 2-year study) remains the most appropriate strategy". Comment: As noted above, extensive research and scientific justification conclude that as with rat carcinogenicity studies, mouse carcinogenicity studies are also not relevant to human health and do not provide added protection in pharmaceutical safety assessment. At the very least, we urge the ICH to recommend the conduct of only one rodent study in cases where the WoE assessment leads to a conclusion of uncertainly regarding human carcinogenicity potential, i.e. either a rat or a mouse carcinogenicity study, depending on which is likely to add the most value to the risk assessment.	Change text to: In cases where the WoE assessment leads to a conclusion of uncertainty regarding human carcinogenicity potential, a 2-year rat carcinogenicity study **or** a carcinogenicity assessment in mice (short term or 2-year study) **may be** the most appropriate strategy.
International Council on Animal Protection in Pharmaceutical Programs (ICAPPP)	76	77	2	Current text: "3) histopathology data from repeated-dose toxicity studies completed with the test agent, with particular emphases on the long term rat study, including exposure margin assessments of parent drugs and major metabolites". Footnote 4: "While long term rat toxicity data are shown to be of highest value for assessing the likely outcome and value of conducting a 2-year rat study, short term rat studies can sometimes also provide histopathologic conclusions of value". Comment: The recommended WoE approach relies heavily on data from "long-term" repeated dose studies, which are not standard toxicology studies. Repeated dose toxicity studies that are required for human pharmaceuticals are typically 28 or 90 days in duration in rodents or 90 days or 9 months in non-rodents (max duration of 6 months is acceptable in the EU). We are concerned that there will be many cases where data from long-term repeated dose toxicity studies do not exist, and a two-year rodent bioassay will be triggered by default. We therefore suggest that the emphasis on long-term studies be removed.	Change text to: "3) histopathology **and/or mechanistic data** from repeated-dose toxicity studies completed with the test agent, including exposure margin assessments of parent drugs and major metabolites". Change text in Footnote 4 to: "Histopathology **and/or mechanistic** findings from repeated-dose toxicity studies of particular interest for identifying carcinogenic potential in a 2-year rat study include cellular hypertrophy, cellular hyperplasia, persistent tumour injury and/or chronic inflammation, foci of cellular alteration, preneoplastic changes, and tumors. It is important to provide an understanding of the likely pathogenesis, and/or address the human relevance of such findings. Data from **repeated-dose** toxicity studies in non-rodents and mice may also be useful for providing additional context on the human relevance of rat study findings (e.g. species-specific mechanistic differences) and whether there is value in conducting a 2-yr rat study".
International Council on Animal Protection in Pharmaceutical Programs (ICAPPP)	93	99	2.1	Current text: "1) additional investigational studies, or analyses of specimens collected from prior studies (e.g., special histochemical stains, molecular biomarkers, serum hormone levels, further characterization of immunomodulation, alternative in vitro or in vivo test systems, data from emerging technologies, etc.)" Comment: The conduct of 'alternative' animal studies should not be encouraged. Instead, the use of more human-relevant methods should be prioritized.	Change text to: "1) additional investigational studies, or analyses of specimens collected from prior studies (e.g., special histochemical stains, molecular biomarkers, serum hormone levels, further characterization of immunomodulation, alternative in vitro, **in silico, grouping and read-across**, data from emerging technologies, etc.)"
International Council on Animal Protection in Pharmaceutical Programs (ICAPPP)	117	121	2.2	Current text: "When the WoE assessment concludes that conduct of a 2-year rat study is not warranted, the Sponsor should seek alignment with the Drug Regulatory Agency [DRA] of each region where marketing approval is sought". Comment: This statement might deter sponsors from choosing to conduct the WoE assessment, as it generates additional action to align with regional DRAs. We recommend a harmonized acceptance of the WoE decision across all regions (e.g. if accepted in the US, the decision should automatically be aligned in acceptance in Japan and the EU).	Change text to: "When the WoE assessment concludes that conduct of a 2-year rat study is not warranted, the Sponsor **should be granted** alignment **across** the Drug Regulatory Agency [DRA] of each region where marketing approval is sought."

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International Council on Animal Protection in Pharmaceutical Programs (ICAPPP)	151	157	2.3	Current text: “A carcinogenicity study in mice, either 2-year or a short-term transgenic model as specified in ICH S1B, remains a recommended component of a carcinogenicity assessment plan, even for those compounds where the integrated WoE assessment indicates a 2-year rat study would not contribute significant value. However, in some cases, for example, when the WoE evaluation strongly indicates no carcinogenic risk to humans and data indicate that only subtherapeutic, pharmacologically inactive drug exposures can be achieved in the mouse, it may not be appropriate to conduct any mouse carcinogenicity study.” Footnote 6: “The WoE approach for the rat is not appropriate for eliminating the mouse as a second rodent carcinogenicity species because: (1) 6-month chronic toxicity studies are not generally conducted with mice so the WoE approach cannot be implemented and no database is available to confirm this approach, (2) the results of carcinogenicity studies in mice will often provide different outcomes from the corresponding rat carcinogenicity study, so a direct extrapolation cannot be made, and (3) a 6-month rasH2-Tg mouse has been adopted as an acceptable carcinogenicity study model”. Comment: As above, we request the ICH to recommend the conduct of only one rodent study in cases where the WoE assessment leads to a conclusion of uncertainly regarding human carcinogenicity potential. Comment on Footnote 6: While the mouse bioassays provide different outcomes to rat bioassays (as to be expected by differences in species physiology and metabolism), both species modes of action are commonly acknowledged not to be relevant to human response.	Change text to: "**In cases where the WoE assessment leads to a conclusion of uncertainty regarding human carcinogenicity potential, a** carcinogenicity study in mice, either 2-year or a short-term transgenic model as specified in ICH S1B, **may be more appropriate than a 2-year rat study.** However, in some cases, for example, when the data indicates that only subtherapeutic, pharmacologically inactive drug exposures can be achieved in the mouse, it may not be appropriate to conduct any mouse carcinogenicity study." Delete footnote 6.