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An agency of the European Union

14 December 2021
EMA/743397/2021

Overview of comments received on ICH guideline M7 on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk – addendum EMA/CHMP/ICH/272147/2021

Please note that comments will be sent to the ICH M7 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

2. Specific comments on text

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
APIC	22	305		As a first note we would like to emphasize that formation of acetaldehyde is inherently part of our production process and the APIs we produce and is not just a simple impurity from e.g. the use of acetaldehyde as solvent and it cannot be removed afterwards. We are under the impression that this type of production (in fact; fermentation) as well as our type of application (parenteral) was not taken into account when writing this draft guideline M7. Therefore we would like to bring our view to your attention regarding a PDE for acetaldehyde for our APIs / applications: In the proposed new version of the ICH M7 guideline a PDE for acetaldehyde for oral and "other routes" is proposed. As our API is being used in parenteral applications (mainly intraperitoneal) this would then fall under "other routes". Therewith toxicity from intraperitoneal application would be regarded similar to toxicity from inhalation application (i.e. the observed carcinogenicity through local irritation as shown in study of Woutersen et al.), which is far from reality. As a result the standard calculation (applying ICH M7 assessment factor of 50,000) leads to an unrealistically low PDE that we consider not relevant for our application (route) and it will be impossible to meet a corresponding limit in the API. Based on our own research a much higher PDE for acetaldehyde for intraperitoneal application is justified due to the mode of action (not a proven genotoxic carcinogen and a limit for mutagenicity applies) and expected local and/or systemic toxicity via this route of administration. The resulting PDE that was calculated is 4.13 mg/day using the alternative calculation method in ICH Q3C(R5) (see attached report of an independent consultant in the column to the right). Our internal risk assessment (related to our registrations) further demonstrates that the API can be used safely when a PDE of 4.13 mg/day is adopted. - CONTINUES -	20322642_CRL_Expert Statement Acetald

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APIC	22	305		- CONTINUATION - A last point of attention is that humans are exposed significantly to acetaldehyde through intake via food, beverages but also alcohol and cigarettes. Given the already significant background concentration a very strict PDE for acetaldehyde in pharmaceuticals given through "other routes" would not be very effective and therefore it is questionable if the current proposal for a specific limit for acetaldehyde in ICH M7 is justified at all. Based on the above our proposal for adaptation of this draft guideline M7 is: 1. Adjust PDE calculation method and establish PDE specifically for parenteral or (at least) intraperitoneal route: not use standard factor of 50,000 but use ICH Q3C(R5) assessment factors for acetaldehyde based on specific mode of action / toxicity (PDE of 4.13 mg/day can be justified), or alternatively (pragmatic solution) 2. Add the parenteral or (at least) intraperitoneal route to the proposed oral route PDE of 2 mg/day.	20322642_CRL_Expert Statement Acetald
APIC	179	179	M7(R2) Addendum, acetaldehyde	The PDE value for oral exposure should also apply to dermal exposure, as a non-linearity of dose-respone can also be expected after topical exposure. Systemic absorption of acetaldehyde after skin contact is likely to be even lower compared to oral ingestion. Alternative: if acetaldehyde is not considered to be a dermal carcinogen, add that dermal exposures to acetaldehyde are not relevant for the risk assessment according to the ICH M7 guideline.	see comment
Janssen	179	179	M7(R2) Addendum, acetaldehyde	The PDE value for oral exposure should also apply to dermal exposure, as a non-linearity of dose-respone can also be expected after topical exposure. Systemic absorption of acetaldehyde after skin contact is likely to be even lower compared to oral ingestion. Alternative: if acetaldehyde is not considered to be a dermal carcinogen, add that dermal exposures to acetaldehyde are not relevant for the risk assessment according to the ICH M7 guideline.	see comment
APIC	757	760	M7(R2) Addendum, formaldehyde	Please include also EFSA (2014) which provides comprehensive and more current data on internal metabolism and turnover. Endogenous turnover of formaldehyde was estimated to be approximately 0.61-0.91 mg/kg bw per minute and 878-1310 mg/kg bw per day assuming a half lifeof 1-1.5 min. Background levels of formaldehyde from food sources (1.7-1.4 mg/kg bw per day for a 60-70 kg person	Add reference and information on endogenous turnover and backgound levels provided in EFSA 2014
Janssen	757	760	M7(R2) Addendum, formaldehyde	Please include also EFSA (2014) which provides comprehensive and more current data on internal metabolism and turnover. Endogenous turnover of formaldehyde was estimated to be approximately 0.61-0.91 mg/kg bw per minute and 878-1310 mg/kg bw per day assuming a half lifeof 1-1.5 min. Background levels of formaldehyde from food sources (1.7-1.4 mg/kg bw per day for a 60-70 kg person Reference: EFSA 2014. Scientific Report. Endogenous formaldehyde turnover in humans compared with exogenous contribution from food sourceshttps. EFSA Journal 2014;12(2):3550, available online, ://www.efsa.europa.eu/de/efsajournal/pub/3550	Add reference and information on endogenous turnover and backgound levels provided in EFSA 2014
APIC	761	761	M7(R2) Addendum, formaldehyde	"formaldehyde can function as the active ingredient in a drug. " to be specified which type of products	Please add finction in the drug
Janssen	761	761	M7(R2) Addendum, formaldehyde	"formaldehyde can function as the active ingredient in a drug. " to be specified which type of products	Please add function in the drug

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
APIC	770	770	M7(R2) Addendum, formaldehyde	"In vivo studies have also detected genotoxic effects primarily at the site of contact". Please add: "always in association of cytotoxicity." Rationale for the amendment as provided in the cited reference (page 156, 2nd para.): " However, the NOEL for respiratory epithelial hyper/metaplasia foundin long-term inhalation toxicity studies in rats suggests that formaldehyde is carcinogenic only at cytotoxic levels,i.e., at levels at which sustained regenerative epithelialproliferation is observed (76 ppm). IARC (2004) concluded that both genotoxicity and cytotoxicity have important roles in the carcinogenesis of formaldehyde in nasal tissues."	Please revise: "In vivo studies have also detected genotoxic effects primarily at the site of contact always in association of cytotoxicity."
Janssen	770	770	M7(R2) Addendum, formaldehyde	"In vivo studies have also detected genotoxic effects primarily at the site of contact". Please add: "always in association of cytotoxicity." Rationale for the amendment as provided in the cited reference (page 156, 2nd para.): " However, the NOEL for respiratory epithelial hyper/metaplasia foundin long-term inhalation toxicity studies in rats suggests that formaldehyde is carcinogenic only at cytotoxic levels,i.e., at levels at which sustained regenerative epithelialproliferation is observed (76 ppm). IARC (2004) concluded that both genotoxicity and cytotoxicity have important roles in the carcinogenesis of formaldehyde in nasal tissues."	Please revise: "In vivo studies have also detected genotoxic effects primarily at the site of contact always in association of cytotoxicity."
APIC	774	775	M7(R2) Addendum, formaldehyde	Whereas IARC assigned formaldehyde to Group 1 (carcinogenic in humans), the EU classified the substance only as a Carc. Cat 1B based on sufficient evidence from animal studies, but only limited evidence of carcinogenicity in humans mainly from the positive association of nasopharyngeal tumours in industrial cohorts (RAC 2012) Ref.: RAC 2012. Committee for Risk Assessment. RAC Opinion proposing harmonised classification and labelling at EU level of Formaldehyd, https://echa.europa.eu/documents/10162/b8dfa022-9544-72e8-dcaa-7491dff3c0d5	Please add: In the European Union formaldehyde is classified as a carcinogen category 1B (May cause cancer). Ref.: Annex VI, Regulation (EC) No 1272/2008 (CLP Regulation), https://echa.europa.eu/de/information-on-chemicals/cl-inventory-database/-/discli/details/55163
Janssen	774	775	M7(R2) Addendum, formaldehyde	Whereas IARC assigned formaldehyde to Group 1 (carcinogenic in humans), the EU classified the substance only as a Carc. Cat 1B based on sufficient evidence from animal studies, but only limited evidence of carcinogenicity in humans mainly from the positive association of nasopharyngeal tumours in industrial cohorts (RAC 2012) Ref.: RAC 2012. Committee for Risk Assessment. RAC Opinion proposing harmonised classification and labelling at EU level of Formaldehyd, https://echa.europa.eu/documents/10162/b8dfa022-9544-72e8-dcaa-7491dff3c0d5	Please add: In the European Union formaldehyde is classified as a carcinogen category 1B (May cause cancer). Ref.: Annex VI, Regulation (EC) No 1272/2008 (CLP Regulation), https://echa.europa.eu/de/information-on-chemicals/cl-inventory-database/-/discli/details/55163
APIC	791	793	M7(R2) Addendum, formaldehyde	In contrast to the IARC assessment, in the EU formaldehyde was not considered a human sytemic carcinogen as concluded in the Opinion of the Committee for Risk Assessment (RAC 2012). Ref.: RAC 2012. Committee for Risk Assessment. RAC Opinion proposing harmonised classification and labelling at EU level of Formaldehyd, https://echa.europa.eu/documents/10162/b8dfa022-9544-72e8-dcaa-7491dff3c0d5	see comment
Janssen	791	793	M7(R2) Addendum, formaldehyde	In contrast to the IARC assessment, in the EU formaldehyde was not considered a human sytemic carcinogen as concluded in the Opinion of the Committee for Risk Assessment (RAC 2012). Ref.: RAC 2012. Committee for Risk Assessment. RAC Opinion proposing harmonised classification and labelling at EU level of Formaldehyd, https://echa.europa.eu/documents/10162/b8dfa022-9544-72e8-dcaa-7491dff3c0d5	see comment

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APIC	854	855	M7(R2) Addendum, formaldehyde	The EU Scientific Committee on Occupational Exposure Limits (SCOEL) concluded in their recommendation of 2016 that " Tumour induction of formaldehyde is driven by sustained cytotoxicity and cell proliferation while genetic changes are secondary. Therefore for formaldehyde a threshold can be established for concentrations not leading to such sustained cell proliferation and histopathological alterations." Ref.: SCOEL/REC/125 Formaldehyde Recommendation from the Scientific Committee on Occupational Exposure Limits, 2016, https://op.europa.eu/en/publication-detail/-/publication/7a7ae0c9-c03d-11e6-a6db-01aa75ed71a1/language-en	Add: SCOEL recommended a Mode of Action based on a threshold for carcinogenicity threshold mechanism (SCOEL 2016).
Janssen	854	855	M7(R2) Addendum, formaldehyde	The EU Scientific Committee on Occupational Exposure Limits (SCOEL) concluded in their recommendation of 2016 that " Tumour induction of formaldehyde is driven by sustained cytotoxicity and cell proliferation while genetic changes are secondary. Therefore for formaldehyde a threshold can be established for concentrations not leading to such sustained cell proliferation and histopathological alterations." Ref.: SCOEL/REC/125 Formaldehyde Recommendation from the Scientific Committee on Occupational Exposure Limits, 2016, https://op.europa.eu/en/publication-detail/-/publication/7a7ae0c9-c03d-11e6-a6db-01aa75ed71a1/language-en	Add: SCOEL recommended a Mode of Action based on a threshold for carcinogenicity threshold mechanism (SCOEL 2016).
APIC	858	861	M7(R2) Addendum, formaldehyde	Oral intake limits for formaldehyde: In addition to the mentioned authorities and organizations, the German Institute for Risk Assessment (BfR) has recently conducted a risk assessment for oral formaldehyde exposure when released from melamin formaldehyde resins. For formaldehyde, the BfR derived an oral Tolerable Daily Intake (TDI) of **0.6 mg per kg of body weight per day** which applies both to local effects and to potential systemic effects of formaldehyde and which was based on long-term studies in rats. This more recent limit is considerably higher than the value proposed by US EPA and Health Canada Ref.: BfR opinion No 046/2019 issued 25 November 2020; Fillable articles made from melamine formaldehyde resin, such as coffee-to-go cups sold as 'bambooware', may leak harmful substances into hot foodsavailable online: DOI 10.17590/20200123-134155; https://www.bfr.bund.de/cm/349/fillable-articles-made-from-melamine-formaldehyde-resin.pdf).	The proposed oral limit of 10 mg/d should be reviewed considering the recent BfR assessment which suggested a Tolerable Daily Intake of 0.6 mg/kg bw/d (ca. 30 mg/day for a human of 50 kg bw)
Janssen	858	861	M7(R2) Addendum, formaldehyde	Oral intake limits for formaldehyde: In addition to the mentioned authorities and organizations, the German Institute for Risk Assessment (BfR) has recently conducted a risk assessment for oral formaldehyde exposure when released from melamin formaldehyde resins. For formaldehyde, the BfR derived an oral Tolerable Daily Intake (TDI) of 0.6 mg per kg of body weight per day which applies both to local effects and to potential systemic effects of formaldehyde and which was based on long-term studies in rats. This more recent limit is considerably higher than the value proposed by US EPA and Health Canada Ref.: BfR opinion No 046/2019 issued 25 November 2020; Fillable articles made from melamine formaldehyde resin, such as coffee-to-go cups sold as 'bambooware', may leak harmful substances into hot foodsavailable online: DOI 10.17590/20200123-134155; https://www.bfr.bund.de/cm/349/fillable-articles-made-from-melamine-formaldehyde-resin.pdf).	The proposed oral limit of 10 mg/d should be reviewed considering the recent BfR assessment which suggested a Tolerable Daily Intake of 0.6 mg/kg bw/d (ca. 30 mg/day for a human of 50 kg bw)
APIC	865	866	M7(R2) Addendum, formaldehyde	The EU Binding Occupational Exposure Limit (BOEL) for formaldehyde of 0.3 ppm (0.37 mg/m3) should be added. Ref.: DIRECTIVE (EU) 2019/983 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 June 2019 amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32019L0983&from=DE	Please add EU BOEL for formaldehyde

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Gilead Sciences	917	928	Addendum	For formaldehyde the limit is 215 ppb or 8 mg/day whichever is lower. As written this will be confusing for implementation. 215 ppb could either be interpreted as concentration of formaldehyde in air, or concentration of formaledhyde relative to drug substance. The calculation on lines 919-928 was developed relative to air concentration. So therefore it should be clarified as 215 ppb in air. The concentration relative to air and relative to drug substance will be substantially different from each other.	Change Line 917 and Formaldehyde table entry to 8,000 mcg/day or 215 ppb (relative to air), whichever is lower (inhalation)
APIC	917	935	M7(R2) Addendum, formaldehyde	Inhalation as well as oral acceptable intakes are overconservative and should consider a) the Mode of Action based on a threshold model (and not more or less a linear modelling) and b) the high endogeneous formation and high oral exposure via food (see EFSA 2014) Reference: EFSA 2014. Scientific Report. Endogenous formaldehyde turnover in humans compared with exogenous contribution from food sourceshttps. EFSA Journal 2014;12(2):3550, available online, ://www.efsa.europa.eu/de/efsajournal/pub/3550	The suggested oral limit of 10 mg/d is suggested to be reviewed based on the EFSA Opinion (2014) and the recent BfR assessment and the suggested Tolerable oral Intake Level of 0.6 mg/kg bw/d (ca. 30 mg/day). Ref.: BfR opinion No 046/2019 issued 25 November 2020; Fillable articles made from melamine formaldehyde resin, such as coffee-to-go cups sold as 'bambooware', may leak harmful substances into hot foodsavailable online: DOI 10.17590/20200123-134155; https://www.bfr.bund.de/cm/349/fillable-articles-made-from-melamine-formaldehyde-resin.pdf). Ref.: EFSA 2014. Scientific Report. Endogenous formaldehyde turnover in humans compared with exogenous contribution from food sourceshttps. EFSA Journal 2014;12(2):3550, available online, ://www.efsa.europa.eu/de/efsajournal/pub/3550
Janssen	917	935	M7(R2) Addendum, formaldehyde	Inhalation as well as oral acceptable intakes are overconservative and should consider a) the Mode of Action based on a threshold model (and not more or less a linear modelling) and b) the high endogeneous formation and high oral exposure via food (see EFSA 2014) Reference: EFSA 2014. Scientific Report. Endogenous formaldehyde turnover in humans compared with exogenous contribution from food sourceshttps. EFSA Journal 2014;12(2):3550, available online, ://www.efsa.europa.eu/de/efsajournal/pub/3550	The suggested oral limit of 10 mg/d is suggested to be reviewed based on the EFSA Opinion (2014) and the recent BfR assessment and the suggested Tolerable oral Intake Level of 0.6 mg/kg bw/d (ca. 30 mg/day). Ref.: BfR opinion No 046/2019 issued 25 November 2020; Fillable articles made from melamine formaldehyde resin, such as coffee-to-go cups sold as 'bambooware', may leak harmful substances into hot foodsavailable online: DOI 10.17590/20200123-134155; https://www.bfr.bund.de/cm/349/fillable-articles-made-from-melamine-formaldehyde-resin.pdf). Ref.: EFSA 2014. Scientific Report. Endogenous formaldehyde turnover in humans compared with exogenous contribution from food sourceshttps. EFSA Journal 2014;12(2):3550, available online, ://www.efsa.europa.eu/de/efsajournal/pub/3550

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APIC	1065	1188	M7(R2) Addendum, styrene	We do not agree with the hazard assessment for styrene that the substance should be considered a genotoxic carcinogen which is relevant for humans. First of all, styrene is not a regulatorily classified carcinogen or mutagen according to GHS or CLP criteria. For example, based on a convincing body of evidence, the European Union hazard classification (CLP regulation) does not recognize styrene as a possible human carcinogen due to the significant physiological differences in styrene toxicity between humans and mice. Styrene was lastly discussed at the EU Committee for Risk Assessment (RAC) at ECHA in 2012 and a classification for mutagenicity or carcinogenicity was not proposed (ECHA 2021; ECHA 2011). We therefore suggest reconsidering the hazard sections on mutagenicity and carcinogenicity in the document taking into account the most recent scientific assessments on styrene. For example, we would like to refer to a comprehensive review by Banton et al. (2019) in which the potential chronic health risks of occupational and environmental exposure to styrene have been evaluated. With regard to a carcinogenic potential, the authors concluded clearly that mechanistic research on mouse lung tumors demonstrates these tumors are mouse-specific and of low relevance to human cancer risk. This assessment is supported by previous assumptions on the potential Mode of Action (e.g., Cohen 2002) Regarding mutagenicity, several critical reviews of the styrene/styrene 7,8-oxide (SO) literature are available from genetic toxicology experts. All concluded that, with the exception of positive in vitro studies, there is little to no convincing evidence that styrene/SO is genotoxic in vivo in rodents (e.g., Moore et al. 2019; Collins and Moore, 2019; Banton et al. 2019). Furthermore, in the most recent EFSA opinion on styrene, the Panel on Food Contact Materials, Enzymes and Processing Aids stated that the IARC conclusions on styrene cannot be directly applied to the evaluation of risks for consumers from the oral exposure to styrene, but also concluded that a concern for genotoxicity associated with oral exposure to styrene cannot be excluded and a systematic review of genotoxicity and mechanistic data, comparative toxicokinetics and analysis of species differences is required for assessing the safety of styrene for its use in food contact materials (EFSA 2020). We therefore propose a review of the present assessment of the mutagenic and carcinogenic potential of styrene with regard to low-dose oral exposure, taking into account all currently available information on toxicological properties and mechsnistic information. -continues-	We suggest reviewing the mutagenicity and carcinogenicity sections considering the provided comments regarding the species-specific MoA of styrene.
APIC	1065	1188	M7(R2) Addendum, styrene	-continuation- References: - Banton at al. 2019. Evaluation of potential health effects associated with occupational and environmental exposure to styrene – an update, Journal of Toxicology and Environmental Health, Part B, 22:1-4, 1-130, DOI: 10.1080/10937404.2019.1633718 - Cohen et al. 2002. A comprehensive evaluation of the potential health risk associated with occupational and environmental exposure to styerene. Journal of Toxico!ogy and Environmental Health, Part B, 5:1-263, 2002 - Collins and Moore 2019. A meta-analysis of epidemiologic studies of occupationally exposed styrene workers and micronuclei levels. Mutat. Res. Genet. Toxicol. Environ. Mutagen. 837:15–28. doi:10.1016/j.mrgentox.2018.08.011 - ECHA 2021. Registry of CLH intentions until outcome, Styrene, available online, https://echa.europa.eu/de/registry-of-clh-intentions-until-outcome/-/dislist/details/0b0236e180a0fa4f - ECHA 2011. CLH report for styrene, Proposal for Harmonised Classification and Labelling, Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2, Substance Name: Styrene, September 2011. available online, https://echa.europa.eu/documents/10162/fd574447-2888-e637-ae30-77df1b043a2f - EFSA 2020. EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP) Assessment of the impact of the IARC Monograph Vol. 121 on the safety of the substance styrene (FCM No 193) for its use in plastic food contact materials. EFSA Journal 2020;18(10):6247 - Moore et al. 2019. Critical Review of Styrene Genotoxicity Focused on the Mutagenicity/Clastogenicity Literature and Using Current Organization of Economic Cooperation and Development Guidance. Environmental and Molecular Mutagenesis 60:624-663	

Name of organisation or individual	Line from	Line to	Section number	Comment and rationale	Proposed changes / recommendation
Janssen	1214	1219	M7(R2) Addendum, styrene	Calculation of an oral limit value: We believe that the proposed calculation of an AI using a linear approach and a TD50 in mice is over-conservative and and inadequate as it does not take into account the species-specific differences for styrene regarding a mutagenic and carcinogenic potential. Based on the above-mentioned mechanistic considerations, we are rather proposing a threshold methodology with non-cancer point of departures and the calculation a PDE value as described in the ICH Q3C and ICH Q3D guidelines.	We suggest the calculation of a PDE value instead of an AI based on the provided comments.
APIC	1332	1336	M7(R2) Addendum, vinyl acetate	It should be added that vinyl acetate is consided to be a locally acting mutagen at the site of first contact at high concentrations, but it does not reach the germ cells. For example, SCOEL concluded in 2005 that "The overall picture obtained from studies of the genotoxicity of vinyl acetate in vivo is that systemic genotoxic effects after ingestion or inhalation were not detected. After high intraperitoneal doses resulting in death, however, an increase in micronuclei in bone marrow cells was observed; this is explained by the saturation of inactivation mechanisms. At high doses, mutagenic effects of vinyl acetate (induced by the metabolite acetaldehyde) on tissues directly exposed locally cannot be excluded." Ref. SCOEL 2005. SCOEL/SUM/122 October 2005.Recommendation from the Scientific Committee on Occupational Exposure Limits for Vinyl Acetate	Please add that vinyl acetate is a locally acting mutagen at the first site of contact, but is not a systemic mutagen.
Janssen	1332	1336	M7(R2) Addendum, vinyl acetate	It should be added that vinyl acetate is consided to be a locally acting mutagen at the site of first contact at high concentrations, but it does not reach the germ cells. For example, SCOEL concluded in 2005 that "The overall picture obtained from studies of the genotoxicity of vinyl acetate in vivo is that systemic genotoxic effects after ingestion or inhalation were not detected. After high intraperitoneal doses resulting in death, however, an increase in micronuclei in bone marrow cells was observed; this is explained by the saturation of inactivation mechanisms. At high doses, mutagenic effects of vinyl acetate (induced by the metabolite acetaldehyde) on tissues directly exposed locally cannot be excluded." Ref. SCOEL 2005. SCOEL/SUM/122 October 2005.Recommendation from the Scientific Committee on Occupational Exposure Limits for Vinyl Acetate	Please add that vinyl acetate is a locally acting mutagen at the first site of contact, but is not a systemic mutagen.
APIC	1433	1433	M7(R2) Addendum, vinyl acetate	Oral limit: It should be added in the document that for consumer products (i.e. plastic materials coming into contact with food) in the EU a Tolerable Daily Intake of 0.2 mg/kg bw/day has been established based on a threshold methodology for calculation of this limit. In the EU Risk Assessment Report for vinyl acetete it is stated on page 88 that " A tolerable daily intake (TDI) value of 0.2 mg/kg bw has been established. " and in notation 11 of the report (same page) it is further explained that " This rather high value was derived by taking the NOAEL and application of safety factors." (EU Risk Assessment Report 2008) According to Regulation (EU) No 10/2011 (PIM), based on this TDI, the specific migration limit for the use of vinyl acetate as FCM (in the EU) is 12 mg per kg of food (Lenzer et al. 2018). Cited in - EU RISK ASSESSMENT report. Vinyl acetate. CAS-No.: 108-05-4.EINECS-No.: 203-545-4, R059_0805_env_hh, 19.08.2008, available onlie, https://echa.europa.eu/documents/10162/23433313-22b7-4e0a-a9d4-b469a451c1cf - Lenzer et al. 2018. CMR substances in consumer products: from food contact materials to toys. Archives of Toxicology volume 92, pages 1663–1671. https://link.springer.com/article/10.1007/s00204-018-2182-3	Please add EU TDI for plastic materials coming into contact with food
APIC	1444	1454	M7(R2) Addendum, vinyl acetate	Please review the suggested AI of 2 mg/day considering the EU TDI for vinyl acetate relevant for plastic materials coming into contact with food. The derivation of a PDE value assuming a threshold MoA is suggested.	see comment

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APIC	1445	1445	M7(R2) Addendum, vinyl acetate	The PDE value for oral exposure should also apply to dermal exposure, as a non-linearity of dose-respone can also be expected after topical exposure. Alternative: if vinyl acetate is not considered to be a dermal carcinogen, add that dermal exposures to vinyl acetate are not relevant for the risk assessment according to the ICH M7 guideline.	see comment
APIC	1457	1477	M7(R2) Addendum, vinyl acetate	**AI for all other routes:** The derivation of an additional AI for the inhalation route is suggested as the inhalative uptake of vinyl acetate can be distinguished e.g. from parenteral administration routes (with a limited data base) due to an expected threshold MoA after inhalation. Several scientific committees and institutions have applied a threshold methodology for derivation of inhalative work place limits. For example, the EU SCOEL concluded in 2008 that "the carcinogenic potential of vinyl acetate is expressed only when tissue exposure to acetaldehyde is high and when cellular proliferation is simultaneously elevated. This mode of action suggests that exposure levels that do not increase intracellular acidification beyond homeostatic bounds will be adequately protective of adverse downstream responses including cancer. This provides the scientific basis to incorporate thresholds for cell proliferation secondary to intracellular acidification. As long as the physiological buffering systems are fully operative, no local carcinogenic effect by vinyl acetate should be expected.Under these considerations of modes of action, a cancer risk at low, non-irritant, concentrations of vinyl acetate in the workplace air appears negligible. The NOAEL for histological changes in respiratory rodent tissues was 50 ppm. A threshold for sensory irritation may be expected to be lower. There are limited observations in humans (ACGIH 1992) of an NOAEL for irritancy at 10 ppm. " Ref. SCOEL 2005. SCOEL/SUM/122 October 2005.Recommendation from the Scientific Committee on Occupational Exposure Limits for Vinyl Acetate	Derivation of a PDE value for inhalation based on a threshold MoA is suggested.
Janssen	1457	1477	M7(R2) Addendum, vinyl acetate	AI for all other routes: The derivation of an additional AI for the inhalation route is suggested as the inhalative uptake of vinyl acetate can be distinguished e.g. from parenteral administration routes (with a limited data base) due to an expected threshold MoA after inhalation. Several scientific committees and institutions have applied a threshold methodology for derivation of inhalative work place limits. For example, the EU SCOEL concluded in 2008 that "the carcinogenic potential of vinyl acetate is expressed only when tissue exposure to acetaldehyde is high and when cellular proliferation is simultaneously elevated. This mode of action suggests that exposure levels that do not increase intracellular acidification beyond homeostatic bounds will be adequately protective of adverse downstream responses including cancer. This provides the scientific basis to incorporate thresholds for cell proliferation secondary to intracellular acidification. As long as the physiological buffering systems are fully operative, no local carcinogenic effect by vinyl acetate should be expected.Under these considerations of modes of action, a cancer risk at low, non-irritant, concentrations of vinyl acetate in the workplace air appears negligible. The NOAEL for histological changes in respiratory rodent tissues was 50 ppm. A threshold for sensory irritation may be expected to be lower. There are limited observations in humans (ACGIH 1992) of an NOAEL for irritancy at 10 ppm. " Ref. SCOEL 2005. SCOEL/SUM/122 October 2005.Recommendation from the Scientific Committee on Occupational Exposure Limits for Vinyl Acetate	Derivation of a PDE value for inhalation based on a threshold MoA is suggested.