ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Substance name: Indium phosphide
CAS number: 22398-80-7
EC number: 244-959-5

General comments

Date	Submitted by Person Organisation/MSCA	Comment	Response	Rapporteur's comments
2009/07/16	Hungary / National Institute of Chemical Safety	In view of the experimental data and the precautionary principle the proposed classification and labelling can be supported.	Thank you for your support.	We have noted the support. We believe the criteria for the proposed classifications are met. The precautionary principle does not apply to C&L.
2009/07/24	Frauke Schröder / Germany / Baua	German CA comment: The following documents were available: 1. Annex XV report, proposal for harmonised classification and labelling, Indium phosphide (May 2009) 2. Outcome of the accordance check of an Annex XV dossier proposing harmonised Classification & Labelling at Community level Indium phosphide reveals convincingly toxicological properties with respect of several toxicological endpoints and a harmonized classification is necessary. However, the justification for the inclusion of R48/23 as an action on a community-wide	The classification proposal for Indium phosphide was initially submitted to ECB and full harmonisation of classification was requested under this context. The classification proposal was not discussed at ECB because of lack of time and it is now submitted to ECHA where only CMR properties and respiratory sensitisation are prioritised for harmonisation. However, we consider that all the relevant data collected within the scope of the previous regulatory context should be used as they are available and show that classification is justified for repeated toxicity. Besides, assessment of repeated toxicity of Indium phosphide is necessary to evaluate the toxicological profile of	The justification given in the BD is weak. However, as discussed here in the COM/RCOM, there are additional reasons supporting a harmonised classification for repeated dose toxicity. The repeated dose pulmonary toxicity is from a mechanistic perspective likely to be related to the carcinogenicity, although not the only reason as tumours are found in other tissues as well. More importantly, a classification with R48/23 will

		basis seems to be insufficient. A possible justification could be that classification for other non-harmonised endpoints (such as repeated inhalation exposure) might be overlooked by notifiers if the substance is already classified as a carcinogen.	the substance in relationship to its carcinogenicity. Therefore, evaluation of R48/23 classification does not bring additional unnecessary work. Besides, we agree with the German comment that repeated inhalation toxicity might be overlooked by suppliers if the substance is only a CMR.	give useful additional information on the route of exposure (inhalation) that may be hazardous, and indicates to exposed people that any pulmonary symptoms could be an alert for too high exposure.

Mutagenicity

Date	Submitted by Person/Organisation /MSCA	Comment	Response	Rapporteur's comments
2009/07 /27	Ireland / Health & Safety Authority	Two in vivo studies are presented. The Annex XV report states:" No classification required" for the endpoint. It is not clear whether the data are presented for information only or whether the French CA have reviewed the data and consider that they do not meet the criteria for classification for mutagenicity. In our opinion, further justification and clarification for this endpoint is required.	Mutagenicity data are presented for information only related to evaluation of carcinogenic properties of indium phosphide. Only repeated toxicity, carcinogenicity and toxicity on fertility are submitted for harmonisation of classification.	It is clear that the mutagenicity data are presented only for information purposes, and that it is not sufficient for deciding on classification.

Carcinogenicity

Date	Submitted by Person/ Organisation/MSCA	Comment	Response	Rapporteur's comments

2009/07/10	Agneta Ohlsson / Sweden / Swedish Chemicals Agency	Cancer The classification as Carc. Cat. 2; R45 is also supported. Tumours are formed in the lungs but also in other organs in rat, mice and hamster in both sexes. The criterion for classification is fulfilled. This is also in agreement with the classification (Group 2A) made by IARC.	Thank you for your support.	The support is noted.
2009/07/06	RIVM / Netherlands	Since the tumours are observed already at a very low dose level and after a short exposure time, it should be considered whether for this compound a specific concentration limit for carcinogenicity should be established.	A proposal to set Specific Concentration Limit (SCL) for carcinogenicity has been added in the Background Document.	A Specific Concentration Limit (SCL) for carcinogenicity on 0.01% has been added to the Background Document, and the SCL is supported.
2009/07/24	Frauke Schröder / Germany / Baua	The German CA supports the proposed classification of Indium phosphide as a presumed human carcinogen Carc. 1B – H350. Based on the CLP regulation category 1B should be applied if the substance is "presumed to have carcinogenic potential for humans, classification is largely based on animal evidence." According to CLP regulation the sufficient evidence of carcinogenicity means that "a causal relationship has been established between the agent and an increased incidence of	Thank you for your support. Further information on dose-response relationship has been added in the Background Document.	The support is noted. The information given suffices for supporting the proposal.

		malignant neoplasms in a) two or more species of animals…" This condition is fulfilled with the increase of lung-tumors in mice, rat and hamsters. However, the transparency and documentation of the available data should be improved for a funded assessment of the studies, especially a detailed dose response relationship with a clear allocation of the effects to the administered doses is necessary. The assessment of the central 2 year rat and mice studies (NTP 2001) was only possible, because these studies were also described in more detail in secondary literature.		
2009/07/27	Ireland / Health & Safety Authority	As discussed above for repeated dose toxicity, we consider that the evaluation of the carcinogenicity proposal is made difficult by the limited study details provided, in particular information on the statistical and/or biological significance of the tumours observed, and information on tumour incidence in the historical control rats of the same strain. We feel that the evaluation is further complicated by the early termination of treatment in the mid and high dose groups in both the	Further information has been added in the Background Document. Indium phosphide induces an increased incidence of alveolar/bronchiolar carcinomas in males and females mice (statistically significant and above historical controls at the low dose), an increased incidence of hepatocellular carcinomas in males and females mice (statistically significant and above historical controls at the low dose), an increased incidence of alveolar/bronchiolar carcinomas in males	The information given suffices for supporting the Carc. Cat. 2-proposal. Detailed information from the NTP-carcinogenicity studies is also easily available on Internet.

		rat and mouse studies, indicating that these animals may have been dosed a higher than the maximal tolerated dose. Therefore, the statistical and biological significance of the tumours observed in the low dose groups becomes critical to the decision as to whether indium phosphide should be classified as Carc. Cat 2 or Cat 3. In the mouse study, while there appears to be an increase in carcinoma of the alveolar and bronchiolar cells, and hepatocellular adenoma and carcinomas in males, the significance of the results in females is not clear. In rats, the increased incidence of tumours in the lung in both males and females and an increase in phenochromocytoma in males appears to be clearer. However, the biological significance of these increases, when compared with the expected tumours at these sites are missing. The significance of the results of the hamster study is not clear. Directive 67/548/EEC requires *"…either positive results in two animal species should be available or clear positive evidence in one species, together with*	and females rats (statistically significant and above historical controls for adenomas and carcinomas incidence at the low dose) and an increased incidence of malignant pheochromocytomas in males rats (not statistically significant but above historical controls at the low dose). Evidence of a carcinogenic effect in these two species therefore support classification in category 2.	

		supporting evidence…" We feel that the proposal for classification as Carc Cat 2 could be strengthened with further information on the statistical and biological significance in tumours observed in the low dose group in both studies. If the significance of the tumours remains unclear, a classification of Carc Cat 3 might be more appropriate.		

Toxicity to reproduction

Date	**Submitted by Person / Organisation/MSCA**	**Comment**	**Response**	**Rapporteur's comments**
2009/07/10	Agneta Ohlsson / Sweden / Swedish Chemicals Agency	Fertility It is not understood why only the tests in male hamsters are relied on for the classification. Adverse reproductive effects are also shown in females not only males. Both in rat and mice ovarian and uterine atrophy was reported. In the rat all animals at 100 mg/m3 dose were affected and in the mouse 4/10 females showed these effects at a dose 30 mg/m3 and 8/10 at 100 mg/m3 dose. In the study with hamsters only males were tested.	Effects were seen in the macroscopic examination and on the weight of reproductive organs of male and female rats and mice in the NTP 14-week inhalation studies. An increase of the estrous cycle length was also seen in female mice at 30 mg/m^3. However, these effects occurred in presence of severe toxicity. In rats, effects occur mainly at 100 mg/m3. At this dose, the final body weight was only 48% of controls in males and 60% in	We agree with the French CA that the general toxicity observed in the mice and rat studies are much too severe to enabling drawing any specific conclusions on reproductive toxicity in these species. A classification with Reps Cat 2 is therefore not warranted. However, as suggested by

		Estrous cycles were altered in female mice. The significant effects on the testis weight, cauda epididymis and epididymis weights were also reported from the rat and mice studies support the findings in the hamster even though they were extensive in the hamster. We agree to that a classification for fertility is justified but a classification as Repr. Cat. 2; R60 should be discussed. Even though a fertility study has not been performed - it is not necessary for classification if other evidences are present - the evidence of adverse reproductive effects occurring at rather low doses (>30 mg/m3) in both sexes in rats and mice (in the hamster study only males were tested), in three different species and together with the kinetic data that indium has a potential to accumulate in the testis the classification in Cat. 2 would be more appropriate.	females, lethargy and hepatic necrosis were observed and toxicity is considered as excessive to draw a conclusion on a potential specific reproductive effect of indium phosphide. Only a decrease of cauda epididymis weigth was observed at 30 mg/m3. The decrease of cauda epididymis weight was similar to the decrease of the body weight and an effect secondary to general toxicity is therefore not excluded. The existence of a specific effect on reproductive function is also not supported by an absence of effect on sperm morphology at this dose. In mice, most of the effects were identified at 30 mg/m3 (parameters not measured at 100 mg/m3). At this dose some mortality was observed in males and females and final body weight was only 66% of controls in males and 71% in females. Lethargy and breathing difficulties were observed and toxicity is considered as excessive. Besides, the decrease of male reproductive organ weight was lower that the general body weight decrease. At 10 mg/m3 only a decrease of testis weight was observed that was less than the decrease of body weight. An effect secondary to general toxicity is therefore not excluded. This is supported by an absence of effect on sperm morphology.	the French CA, the results from the rats and mice studies could perhaps support classification with Repr Cat 3 based on the hamster study.

			Due to massive toxicity, it is not clear whether adverse effects on reproductive organs in mice and rats were specific or secondary to toxicity. The results of the rats and mice studies are used as a supportive evidence for classification, which is mainly based on the hamster study that investigates only male reproductive system. The interpretation of hamster study is however limited by the single dose used in study design and the low number of animals used (4 to 8 per time point) and no evaluation of fertility itself is available. A classification in category 3; R62 is therefore considered appropriate based on a weight of evidence approach.	
2009/07/24	Frauke Schröder / Germany / Baua	The German CA agrees on the basic idea of classifying the substance as a reproductive toxicant on the basis of effects in the reproductive organs (i.e. degeneration of testicular epithelium, uterine degeneration). However, the classification proposal category 2 for reproductive properties Repr. 2 – H316f would benefit from more details on the study results. Quantitative data on body weight changes and organ toxicity could also allow to analyse contribution of general	Further data on the rat and mouse 14-week studies have been added in the Background Document.	Some additional data has been given.

		toxicity on testis toxicity and female reproductive toxicity in the rat and mouse (14-week-) inhalation studies (NTP, 2001).		
2009/07/27	Ireland / Health & Safety Authority	We agree that any effects observed in the reproductive organs in the mouse and rat repeated dose toxicity studies occurred at doses which induced severe systemic toxicity and therefore, the key study for this endpoint is the eight week hamster study. In this study, testis and epididymis weights and caudal sperm counts are reduced but appear to be reversible in that they return to control levels in line with body weight changes at the end of 88 week observation period. There appears to be some evidence of systemic toxicity in these animals and we note also that histopathological effects were observed. We consider that the limited data provided makes evaluation of this endpoint difficult. In our opinion, further information on the histopathological observations, including when these were observed, and the severity of both the affects observed and the systemic toxicity, is missing from the evaluation.	Further information has been added in the Background Document.	Some additional data has been given, but is also noted that the hamster study is reported in 2 papers available in the open literature (Yamazaki et al 2000, Omura et al 2000). It is clear from the data that body weight gain is slightly reduced by the exposure to indium phoshide, leading to lower body weights of the exposed animals during the study. The two papers are not very thorough, and when it comes to effects on body weights not internally consistent. At the end of the exposure period the difference in body weight is statistically significant according to Yamazaki et al (2000), by some 6% as estimated from figure 1A of that report, whereas no

		Also, given the reliance on the hamster study for this endpoint, we consider that a comment regarding the quality of the data would also be beneficial. Without this key information, we are not in a position to reach a decision on the proposal to classify indium phosphide as Repr. Cat 3 R62.		difference was seen in body weights according to Omura et al (2000). Furthermore, Yamazaki reports a maximally 6% lower body weight at week 16 post-exposure, whereas figure 1B of the same paper indicates that the body weight is perhaps 13% lower than in the controls during quite a large period of the post-exposure period. Omura, on the other hand, indicates that the body weights of the exposed group is 10-20% lower than of the control group from week 8-64 post exposure. The animals clearly suffer from the pulmonary toxicity of indium phosphide, and it is difficult to assess the health status of the animals, although no systemic signs of general toxicity were observed. Effects on the male reproductive tract of the hamster are indicated by;

				• the sperm count at the end of the exposure period was reduced (by 10%) more than the body weight, and the sperm count was maximally reduced by 60% by week 64, • the weight of the testis and epididymes being much more reduced (maximally 40%) than the body weight, • by histopathological changes in the testis (from vacuolization of seminiferous epithelium to atrophy of seminiferous tubules), • effects being relatively consistent over time during the 88 weeks post-exposure period. Some support is also provided by the observation that indium phosphide accumulates in the rat testis over time, even after

				exposure has ended. NTP (2001) briefly reviewed reproductive/developmental toxicity studies performed using different indium-compounds, but there are no indications of testicular toxicity caused by e.g. indium trichloride. Testicular toxicity was, however, indicated for indium arsenide in the Omura study (2000), although in the presence of a body weight reduction by some 30%. Read-across arguments are therefore of no use in this case. In spite of the draw-backs of the hamster study (e.g., only one dose level was studied), we support the proposal to classify indium phosphide for reproductive toxicity, Repr Cat 3 R62.

Other hazards and endpoints

Date	Submitted by Person / Organisation/MSCA	Comment	Response	Rapporteur's comments
2009/07/10	Agneta Ohlsson / Sweden / Swedish Chemicals Agency	The classification with T; R48/23 is supported. The chronic inflammation and other severe lesions in the lung and also the hepatocellular necrosis at low doses in two species are in support of this classification	Thank you for your support.	The support is noted.
2009/07/06	RIVM / Netherlands	Since serious lung damage is observed already at a dose level of 0.1 mg/m3 after 21 weeks, it should be considered whether for this compound a specific concentration limit for should be established.	No guidelines are available at this time to set specific concentration limits for repeated toxicity and guidelines should be awaited to ensure harmonisation of the method used.	Based on the CLP guidance, specific concentration limits have been calculated by the rapporteurs also for repeated dose toxicity.
2009/07/24	Frauke Schröder / Germany / Baua	The German CA supports the proposed classification of Indium phosphide regarding the specific target organ toxicity STOT Rep. 1 – H372. Based on the significant increase of fibrosis in the lung of experimental animals at low Indium phosphide concentrations (0.03 mg/m3) we endorse the proposal. Relating to physicochemical	Thank you for your support. The information has been added in the	The support is noted. The physicochemical

		characteristics: The property "Flammability" should be complemented with: evolves flammable gas (PH3) in contact with water or humid air.	Background Document.	properties should not be discussed as there is no classification proposal for them, but we support the revised text.
2009/07/27	Ireland / Health & Safety Authority	We consider that the level of detail included in the study summaries presented in the Annex XV report makes evaluation of this endpoint difficult. In particular no information is provided on the test methods and the GLP status of the studies. Also, the type, severity and biological and/or statistical significance of the key effects observed is not always clear from the study summaries. While it is stated that in the 12 week inhalation studies, in particular in mice, deaths occurred at the who highest dose groups (30 & 100 mg/ m3), the severity of the effects observed in the lower dose groups in these studies are not clear. Also, no NOAEL values were reported for the repeated dose toxicity studies and thus, comparison with the classification criteria is difficult. In the 14 week study in mice (National	Further information has been added in the Background Document. However, NOAEL were not added as they are not relevant for classification. Classification is based on the lowest dose inducing serious damages.	The information given suffices for supporting the R48/23-proposal.

		Toxicology Program, 2001), it states"Lungs are discoloured and enlarged. Inflammation is more severe than in rats" but there is no indication of which dose groups this effect was observed in and if inflammation was observed in all dose groups, whether the severity was the same or whether a dose response was observed. However, from the limited information provided, there appears to have been a severe inflammatory response in the lung (including interstitial regenerative fibrosis) observed in all treatment groups (1,3,10,30 and 100 mg/m3) in the 14 week study in rat. There was also evidence of severe lung inflammation in the 2 year studies, although the severity in rats is not clear. In presenting the justification for classification, it may have been beneficial if doses (and NOAELS if any) had been presented in the same units as those for the classification cut-off values to allow easy comparison with the classification criteria. According to Directive 67/548/EEC, the criterion for		

		application of R48/23 is: Inhalation rat ≤ 0,025 mg/l, 6 hr/day (based on a 90-day study). However, overall, based on mortality and moribund condition observed at 30 mg/m3 and above, and severity of the inflammatory response in the lungs (including fibrosis) at lower doses in the 14 week rat study, we can agree to classify the substance as T R48/23. Under CLP Regulation, the classification criteria cut-off values for STOT RE (inhalation) vary slightly depending on whether the test substance is a gas, vapour or dust/mist/fume. Therefore, it is suggested that the justification for STOT RE is clarified, to include which value is applicable.		We note the support. The NTP-studies are conducted using ”particulate aerosols”, and the criteria cut-off values (classification threshold) for 14 weeks studies given in the report are therefore correct. However, the values have been recalculated to correspond with a chronic exposure situation by dividing with 8 without explaining where the factor 8 comes from. As there is no specific guidance for this extrapolation (using Haber’s law would give a lower number), we suggest to just mention that the threshold would be lower based a 2-year study but that the data anyway clearly fulfill the thresholds for classification.