Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

pirimicarb (ISO); 5,6-dimethyl-2-dimethylamino-pyrimidin-4-yl N,N-dimethylcarbamate

EC number: 245-430-1
CAS number: 23103-98-2

CLH-O-0000001412-86-39/F

Adopted

4 December 2014

04 December 2014

CLH-O-0000001412-86-39/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: pirimicarb (ISO); 5,6-dimethyl-2-dimethylamino-pyrimidin-4-yl N,N-dimethylcarbamate

EC number: 245-430-1
CAS number: 23103-98-2

The proposal was submitted by the **United Kingdom** and received by the RAC on **21 July 2014.**

In this opinion, all classifications are given in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonised System (GHS). The classification notation for 67/548/EEC, the Dangerous Substances Directive (DSD) is no longer provided.

PROCESS FOR ADOPTION OF THE OPINION

The **United Kingdom** has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation*** on **04 June 2014**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by 21 July 2014

ADOPTION OF THE OPINION OF THE RAC

Rapporteurs, appointed by RAC: **Veda Varnai**

Co-rapporteur: **Pietro Paris**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling of pirimicarb was reached on **04 December 2014** and the comments received are compiled in Annex 2. The RAC Opinion was adopted by **consensus.**

OPINION OF THE RAC

The RAC adopted the opinion that **Pirimicarb (ISO)** should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

Annex VI	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard Statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Entry	006-035-00-8	pirimicarb (ISO); 5,6-dimethyl-2-dimethylamino-pyrimidin-4-yl N,N-dimethylcarbamate	245-430-1	23103-98-2	Acute Tox. 3 * Aquatic Acute 1 Aquatic Chronic 1	H301 H400 H410	GHS06 GHS09 Dgr	H301 H400 H410			
Dossier submitter proposal	006-035-00-8	pirimicarb (ISO); 5,6-dimethyl-2-dimethylamino-pyrimidin-4-yl N,N-dimethylcarbamate	245-430-1	23103-98-2	**Add:** Carc. 2 Acute Tox. 3 Skin Sens. 1B **Modify:** Acute Tox. 3 **Retain:** Aquatic Acute 1 Aquatic Chronic 1	**Add:** H351 H331 H317 **Retain:** H301 H400 H410	**Add:** GHS08 **Retain:** GHS06 GHS09 Dgr	**Add:** H351 H331 H317 **Retain:** H301 H410		**Add:** M=10 M=100	
Proposal for RAC	006-035-00-8	pirimicarb (ISO); 5,6-dimethyl-2-dimethylamino-pyrimidin-4-yl N,N-dimethylcarbamate	245-430-1	23103-98-2	**Add:** Carc. 2 Acute Tox. 3 Skin Sens. 1 **Modify:** Acute Tox. 3 **Retain:** Aquatic Acute 1 Aquatic Chronic 1	**Add:** H351 H331 H317 **Retain:** H301 H400 H410	**Add:** GHS08 **Retain:** GHS06 GHS09 Dgr	**Add:** H351 H331 H317 **Retain:** H301 H410		**Add:** M=10 M=100	
Resulting Entry	006-035-00-8	pirimicarb (ISO); 5,6-dimethyl-2-dimethylamino-pyrimidin-4-yl N,N-dimethylcarbamate	245-430-1	23103-98-2	Carc. 2 Acute Tox. 3 Acute Tox. 3 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H351 H331 H301 H317 H400 H410	GHS06 GHS08 GHS09 Dgr	H351 H331 H301 H317 H400 H410		M=10 M=100	

RAC general comment

Pirimicarb, a pesticidal active substance, has been reviewed under Directive 91/414/EEC with the UK as the Rapporteur Member State. In addition to the existing classification (Acute Tox 3 *; H301, Aquatic Acute 1; H400 and Aquatic Chronic 1; H410), a proposal to add Acute Tox 3; H331 and Skin Sens 1; H317 was discussed and agreed by the Technical Committee on Classification and Labelling (Directive 67/548/EEC) in May 2007. Following reanalysis of available data during the preparation of the CLH report, the dossier submitter (DS) also proposed to remove the minimum classification for acute toxicity by the oral route and to add classification for carcinogenicity as Carc 2; H351.

RAC evaluation of acute toxicity

Summary of the Dossier submitter's proposal

Three acute toxicity studies were presented in the CLH report. Studies were conducted by oral, inhalatory and dermal routes in the Wistar-derived SD rat strain.

In an acute oral toxicity study in rats in accordance with OECD Test Guideline (TG) 401, LD_{50} values were calculated to be:

- 152 mg/kg bw in males and
- 142 mg/kg bw in females.

Clinical signs of toxicity were observed at all doses from the first day of treatment, and were characteristic of poisoning with an acetyl cholinesterase inhibitor (including salivation, irregular breathing, diarrhoea, fasciculation, upward curvature). The DS proposed that according to the CLP criteria, the current classification for pirimicarb in the acute oral toxicity hazard category 3 ($50 < ATE \leq 300$) and with the hazard statement H301: Toxic if swallowed should remain, but with the removal of the minimum classification (*) for acute toxicity.

In an acute dermal toxicity study in rats (in accordance with OECD TG 402), no animals died and there were no signs of systemic toxicity with the applied dose of 2000 mg/kg bw (limit test, 24-hr exposure). Local skin irritation (desquamation and some small scabs) was observed at the application sites of one out of 5 males and two out of 5 female rats.
No classification for acute dermal toxicity was proposed by the DS ($LD_{50} > 2000$ mg/kg bw).

In an acute inhalation toxicity study (in accordance with OECD TG 403), rats were exposed for 4 hours nose-only, to pirimicarb aerosol with particle size distribution within the recommended range (the mass median aerodynamic diameter (MMAD) ranged from 3.02 µm to 3.46 µm, with a geometric standard deviation from 1.89 µm to 2.04 µm). LC_{50} values were calculated to be:

- 0.948 mg/L in males and
- 0.858 mg/L in females.

Clinical signs of toxicity, characteristic for poisoning with an acetyl cholinesterase inhibitor, were observed at all doses during or immediately after exposure. The DS proposed that according to the CLP criteria, pirimicarb should be classified in the acute inhalation toxicity hazard category 3 ($0.5 < ATE \leq 1.0$, for dusts and mists), with the hazard statement H331: Toxic if inhaled.

Comments received during public consultation

Four MSCA supported the proposed classification during public consultation.

Assessment and comparison with the classification criteria

Following a comparison of the available acute oral LD_{50} and inhalation LC_{50} values with the classification criteria, RAC supports the conclusion of the DS that according to the CLP Regulation, pirimicarb should be classified as **Acute Tox. 3 - H301** (Toxic if swallowed) with the removal of the minimum classification (*) and as **Acute Tox. 3 - H331** (Toxic if inhaled).

RAC evaluation of skin sensitisation

Summary of the Dossier submitter's proposal

One skin sensitisation study in accordance with OECD TG 406 (Magnusson and Kligman maximisation test) was conducted using female Guinea pigs (Dunkin-Hartley strain, 20 exposed and 10 control animals). Intradermal induction was performed with 3% dilution and epidermal induction with 75% dilution of pirimicarb in corn oil. Challenge was performed by applying 30% and 75% pirimicarb dilution on the right and left flank, respectively. In animals challenged with 30% pirimicarb dilution, positive reaction (scattered mild redness, intense redness and swelling) was found in 32% of animals (6 out of 19; one animal with slipped bandage was excluded) at the 24 hr reading, and in 47% of animals (9 out of 19) at the 48 hr reading. In animals challenged with 75% pirimicarb dilution, positive reaction (scattered mild or moderate diffuse redness) was found in 21% of animals (4 out of 19) at the 24 hr reading, and in 32% of animals (6 out of 19) at the 48 hr reading (see the table below).

Time after challenge	Pirimicarb dilution at challenge		Negative control
	30%	75%	
24 hours	6/19* (32%)	4/19 (21%)	0/10
48 hours	9/19 (47%)	6/19 (32%)	0/10

*One animal exposed to pirimicarb was excluded due to slipped bandage.

A positive control study, performed 21 months before this study, showed positive reaction to formaldehyde in 94% of animals. No positive result was observed in negative controls. The DS concluded that since the induction dose of 3% pirimicarb dilution caused a positive response in more than 30% of animals, pirimicarb should be classified as Skin Sens. Cat. 1; H317. The DS further proposed sub-category 1B, with the justification that pirimicarb did not produce a sensitising response ≥ 60% at the induction dose of 3%.

Comments received during public consultation

Four MSCAs supported the proposed classification (Skin Sens. 1B; H317), and one of them requested additional clarification on the way of choosing test substance concentrations for the induction and challenge exposure and whether any skin irritation was observed during the induction phase.

Assessment and comparison with the classification criteria

The available skin sensitisation study was conducted in accordance with OECD TG 406, with the possible deviation that during topical induction mild-to-moderate skin irritation was probably not produced after topical induction but this was not reported either in the CLH report or in the DAR. Namely, pirimicarb was not irritant to the skin (according to skin irritancy test), the same dilution was applied for topical induction and challenge (75% dilution; challenge dose should be the highest non-irritant dose), and application of a skin irritant (sodium lauryl sulphate) prior to topical induction was not reported either in the CLH report or in the DAR.

Nevertheless, the study is regarded as acceptable and the proposed classification, Skin Sens. Cat. 1; H317, is supported by RAC since a positive skin reaction was observed in more than 30% of exposed animals. RAC, however, does not support the proposed sub-categorisation (1B) since the intradermal induction dose was above 1% and the decision regarding sub-categorisation in 1A could not be made. The classification criteria for sub-category 1B are met according to the criteria laid down in the 2nd Adaptation to Technical Progress (ATP) to the CLP Regulation, since ≥ 30% animals responded at > 1% intradermal induction dose. The positive response rate at 3% induction dose is lower than 60% (21% to 47%) and thus does not suggest that it can be ≥ 60% at ≥ 0.1% to <1% induction dose, or ≥ 30% at ≤ 0.1% induction dose. However, the possibility of a response rate compliant with sub-category 1A cannot be completely excluded since there are no experimental data with an induction dose below 1%. RAC concludes that pirimicarb should be classified as Skin Sens. 1 (H317) without sub-categorisation.

RAC evaluation of carcinogenicity

Summary of the Dossier submitter's proposal

Out of two carcinogenicity studies available in rats and three carcinogenicity studies available in mice, only one rat study and two mice studies were considered reliable by the DS. The findings of one rat study and one mouse study have been rendered unreliable due to poor study designs and an outbreak of respiratory disease with high mortality and antibiotic treatment. The reliable carcinogenicity studies provided the basis for the classification proposal by the DS.

Two-year oral study in rats (Tinton, 1992)

The study was performed in accordance with OECD TG 453 with Alderley Park (Sprague Dawley derived) rats, 64 per sex/dose (0, 75, 250 and 750 ppm pirimicarb in the diet, corresponding to 0, 3.7, 12.3 and 37.3 mg/kg bw/d in males and 0, 4.7, 15.6 and 47.4 mg/kg bw/d in females), of which 11 or 12/sex/dose were sacrificed at week 52. In an additional satellite group (36/sex/dose - with 8/sex/dose being sacrificed at weeks 27, 53, 79 and 105), plasma, erythrocyte and brain cholinesterase activity was determined.

Mortality

After approximately one year of treatment, high mortality was observed in males in all treatment groups (52% to 65%) and in the controls (58%), and somewhat lower in females (29% in controls, 31% to 38% in exposed groups). Mortality rates were not dose-related and followed a similar time pattern. Therefore, they were not considered treatment-related. No evidence of disease or infection that might have compromised the findings of this study was observed.

General toxicity

During the course of the study, at 250 and 750 ppm a reduction in body weight gain (up to 13% in males and 19% in females), reduced food consumption (at 750 ppm) and changes in haematological parameters (increased mean cell volume and mean cell haemoglobin in males; increased haemoglobin, haematocrit and mean cell haemoglobin in females) and biochemical parameters (increased plasma cholesterol and triglycerides, decreased alkaline phosphatase, in both sexes) were observed. At 750 ppm, increased relative liver weights (9.2% in males, 11.7% in females) were measured. There were no treatment-related clinical signs.

Acetyl cholinesterase activity

Plasma cholinesterase activity was consistently reduced (up to 28%) in females and occasionally in males (up to 27%) at 250 and 750 ppm. Brain and erythrocyte cholinesterase activities were not affected, but the time between sampling and cholinesterase activity analysis was not precisely reported.

Non-neoplastic effects

An increase in the incidence of necrosis of the brain, vacuolation of the adrenal cortex, pelvic vascular ectasia, kidney transitional cell hyperplasia, voluntary muscle degeneration, minimal hepatocyte hypertrophy and minimal to slightly altered hepatocytes (clear cell), were observed in males (mainly at the top dose), as well as an increase in severity of sciatic nerve demyelination (at the top dose). There was no association between astrocytoma and brain necrosis.

In female rats, there was an increased incidence of kidney transitional epithelial hyperplasia and pelvic vascular ectasia (at the top and mid dose), and increased incidence of voluntary muscle degeneration and severity of sciatic nerve demyelination (at the top dose).

Sciatic nerve, voluntary muscle, adrenal cortex and kidney changes were interpreted as a treatment-related exacerbation of spontaneous age related changes.

Regarding neoplastic effects, a dose-related increase in the incidence of astrocytoma in males and uterine stromal cell polyp in females was observed. In addition, increased incidence of meningioma in the mid dose males and top dose females, and uterine stromal cell sarcoma and mammary gland fibroadenoma in top dose females, was found (Table 1 in the Section "Supplemental information" in the background document). Nevertheless, the DS reported that these tumours are unlikely to be treatment-related because they were within the historical

control range (Table 5 in "Supplemental information") and/or did not follow a dose-response pattern:

- Astrocytoma: Incidence in male and female rats was at the upper limit of the historical control range (0-5.8% for the same strain, years 1982-1992), and in the females it did not follow a dose-related pattern.
- Meningioma: The increases exceeded the male and female historical control range (0-1.9%), but did not follow a dose response pattern in males and the incidence observed in females at the top dose (3.8%) was the same as for male controls (which was also above the historical control range).
- Uterine stromal cell polyp: The incidences were within the historical control range (0-23.1%).
- Uterine stromal cell sarcoma: An increased incidence was observed only at the top dose and was within the historical control range (0-3.8%).
- Mammary gland fibroadenoma: The incidences did not follow a dose-related pattern and were within the historical control range (3.8-19.2%).

Two-year oral study in rats (Samuels, Hodge and Palmer, 1975)
The results of this study are provided for information as they are considered unreliable. The study design comprised three experiments:
1) male Sprague-Dawley rats, 48 animals/dose, dosed at 0, 750 or 2500 ppm;
2) male Wistar-derived rats, 48 animals/dose, dosed at 0, 750 or 2500 ppm;
3) Wistar-derived pregnant rats fed at 0 or 750 ppm of pirimicarb, their offspring (24/sex/dose) dosed at 0 or 750 ppm for 2 years.

In this study, increased incidences of reticulum cell lymphoma of the lung in Sprague-Dawley rats (2.1%, 8.3% and 13% at 0, 750 and 2500 ppm, respectively) and mammary gland fibroadenoma in Wistar rats (17% and 29% at 0 and 750 ppm, respectively) were observed. The findings from this study are not considered reliable due to high mortality rate (up to 85%) caused by a respiratory disease (started after 40 to 50 weeks of exposure, unsuccessfully treated with antibiotics) and poor study design (small group sizes, only two doses tested in the third experiment, unspecified antibiotic treatment). Reticulum cell lymphoma of the lung was suggested (by the study authors) to arise in peribronchial lymphoid tissue due to chronic respiratory infection, and mammary gland fibroadenoma incidences were within the historical control range for females of this strain (18-45%, total incidence 36.1%).

Heighty-week oral study in mice (Rattray, 1998)
The study was performed in accordance with OECD TG 451 in C57BL/10JfCD-1 Alpk (C57 black) mice, 55/sex/dose (0, 50, 200 or 700 ppm corresponding to 0, 6.7, 26.6 or 93.7 mg/kg bw/d in males and 0, 9.0, 37.1 or 130.3 mg/kg bw/d in females). This study was conducted because the older 80-day oral study in Alderley Park mice (Palmer and Samuels, 1974) was considered unreliable since it was a non-guideline and non-GLP study and an outbreak of respiratory disease with high mortality occurred. In the new study, a C57 black mouse strain was used because it has lower and less variable spontaneous incidence of lung and liver tumours compared to Alderley Park Swiss derived strains.

Mortality
Survival was > 85% across all dose groups. There were no treatment-related effects on mortality.

General toxicity
During the course of the study (weeks 2-81), reduced body weight (up to 5.5% in males and up to 8% in females) was observed at the top dose (700 ppm) (Table 2 in "Supplemental information"). Reduced food consumption (up to 9.5%) in males, reduced food utilisation in both sexes (by 21% in males and 13.3% in females, weeks 1-12), increased incidence of subcutaneous masses and eye discharge in females, were also found at this dose level. Subcutaneous masses were not related to adverse histophatological changes. Regarding haematological parameters (see Table 2 in "Supplemental information"), a dose–related increase in red blood cell (RBC) count and decrease in mean cell volume (MCV), mean cell haemoglobin (MCH) and mean cell haemoglobin concentration (MCHC) was observed in both

sexes. Haemoglobin levels, however, remained unchanged across study groups. At the top dose, an increase in platelet count was found in females. Absolute and relative liver weights were increased at 200 and 700 ppm in both sexes, but there were no associated pathological microscopic changes.

Non-neoplastic effects
A slight increase in the incidence of interstitial mononuclear cell infiltration in the kidney was observed in both sexes at the top dose. An increase in the incidence of pelvic mononuclear cell infiltration in the kidney was dose-related in males, and in the females was observed at the mid dose (200 ppm). Lymphoid proliferation in the lungs increased in a dose-related pattern in females. An increase in spleen pigmentation incidence, observed in top dose females, was in the study report described as melanin deposition, spontaneously occurring in this strain of mice.

The incidence of lung adenoma was increased in males and females at the top dose (5.5% *vs.* max. 1.8% in all other male groups; 10.9% *vs.* 0% max. in all other female groups; see also Table 2 in "Supplemental information" in Annex 2). In females at the top dose, one case of keratinising squamous lung epithelioma was recorded.

Lung adenoma in males was within the historical control range for this strain (1.8-7.3%, median 2.8%). However, in the females the incidence of 10.9% at the top dose was markedly higher than the upper value of the historical control range for female mice of the same strain (0-3.6%, median 1.8%), and was therefore considered as treatment-related by the DS. A single incidence of benign keratinising squamous epithelioma at the top dose was considered to be supportive of a treatment-related effect in the lungs. The DS mentioned that the dose level of 700 ppm does not exceed the maximum tolerated dose (MTD), since the observed effects are not sufficiently severe.

Lifetime feeding study in mice (Sotheran et al., 1980)
A life time feeding study (94-96 weeks) in mice (Sotheran *et al*., 1980) was performed in accordance with OECD TG 451 (non-GLP study), in 60 Alderley Park Swiss-derived mice/sex/dose (0, 200, 400 or 1600 ppm; food consumption was difficult to measure due to large amounts of food wastage that was often damp when weighed).

Mortality
During weeks 30 to 60 and shortly before termination, the mortality rate increased in females at 1600 ppm (up to 89%). Other groups did not differ in mortality rates compared to controls (Figure 2 in Supplemental information). Terminal kills were made when mortality approached 80%, i.e. in week 94 for females and week 96 for males.

General toxicity
There were no specific clinical signs related to treatment, but the top dose (1600 ppm) animals of both sexes showed reduced body weight gain during the experiment (Figure 3 in "Supplemental information"). Reduced body weight gain was also observed at 400 ppm, but only during the first 8 weeks of the study.
Food consumption and food utilisation was reduced in males and females at 1600 ppm.

Non-neoplastic effects were not observed at microscopic tissue examination.

Increased incidences of lung adenomas were observed in males at 1600 ppm (29.2%) and females at 400 and 1600 ppm (18.6% and 30.5%, respectively). These values were also above the historical control range (males: 6.6-18.3%, median 10.7%; females: 0-13.3%. median 6.7%, years 1978-1983). Nevertheless, the highest dose, 1600 ppm, exceeded the MTD (markedly reduced body weight gain during the study).

Liver hyperplastic nodules and benign tumours increased in incidence which exceeded the historical control range (males: 8-21.7%, median 14.4%; females: 0-3.3%, median 2.0% in females) in males treated with 1600 ppm (26.3%) and in all exposed females (3.5% to 10.3%), but without a dose response relationship. There was also an increased in the incidence

of liver tumours with signs of malignancy. The incidence exceeded the historical control range (8.3-18%, median 14.5%) in males at 200 and 1600 ppm (22.0% and 29.8%, respectively) and in females dosed at 1600 ppm (8.5%; historical control range 0-8.3%, median 3%). Although, the increase in both types of tumours was above the historical control range, it did not follow a dose-response pattern and no pre-neoplastic lesions were reported. The DS, therefore, concluded that the increase in liver tumours observed in this study provides limited evidence of carcinogenicity.

The incidence of lymphosarcoma was rather high, but equally distributed across study groups in both sexes. Therefore, it is not considered substance-related. The incidence of mammary gland adenocarcinoma was above the historical control range only at the highest dose, considered to exceed the MTD. Therefore, this tumour is considered to provide limited evidence of carcinogenicity.

In addition, ovary tumours and papillary cystadenoma were also increased. Papillary cystadenomas (a benign epithelial tumour) were observed at doses of 400 and 1600 ppm. The incidences exceeded both concurrent (0%) and historical controls (0-2.1%, median 0). The DS considered that in the absence of mechanistic data to explain the observed increase of this tumour type in female Alderley Park mice, these tumours are considered to be treatment related.

Eighty-week oral study in mice (Palmer and Samuels, 1974)
In an older, unreliable 80-week oral study in mice (Palmer and Samuels, 1974), Alderley Park mice (50/sex/dose) were dosed at 0, 300 or 1500 ppm pirimicarb in diet. In males and females, a dose-dependent increase in the incidence of pulmonary adenoma was observed (Table 4 in "Supplemental information"). However, since this is not a guideline or GLP study, and an outbreak of respiratory disease with high mortality (despite the treatment with tetracycline or sulphadimidine) occurred, these findings are taken with caution by the DS.

Supportive information from repeated dose toxicity and genotoxicity studies
Pre-neoplastic lesions were not reported in a 90-day oral study in rats. In other rat studies it was not stated that histopathology examination was performed. In dog studies, histopathological changes were related to haemolytic anaemia not observed in rodent studies. Since these studies are presented only as supportive information for carcinogenic toxicity evaluation, no classification is proposed for repeated dose toxicity.
The DS concluded that the potential genotoxicity of pirimicarb has been well investigated in *in vitro* and *in vivo* assays. The only positive result, indicative of a clastogenic effect, was found in some replicates of the TK+/- mouse lymphoma assay in the presence of S9 metabolic activation. Genotoxic effect, however, was not confirmed in other *in vitro* tests (bacterial reverse mutation tests, mammalian chromosome aberration test), or in *in vivo* studies (mouse micronucleus test, UDS in rat liver, dominant lethal assay) (for a more detailed description, please see "Supplemental information"). Since these data are given as supportive information only, no classification is proposed for mutagenicity.

The DS concluded that considering all available data, pirimicarb demonstrated limited evidence of carcinogenicity in animals. Tumours that are considered treatment-related are:

- lung adenoma in females C57 black mice at the top dose (markedly higher than the upper value of historical control range);
- ovary tumours - papillary cystadenoma in Alderley Park mice observed at mid and top dose (exceeded both concurrent and historical controls).

The increase in liver tumours (in low and top dose males and top dose females) and mammary gland adenocarcinoma (in top dose females) observed in a life-time feeding study in Alderley Park mice, provides only limited evidence of carcinogenicity.

Several factors weaken the available evidence: the treatment related tumours were reported only in one species (mice) and one sex (females); many tumour incidences exceeded the historical control range only at doses above the MTD (mammary gland adenocarcinoma and pulmonary adenomas in Alderley Park mice); pre-neoplastic lesions were not reported (ovary

tumours in Alderley Park mice); a clear dose-response pattern was not observed (liver tumours in Alderley Park mice).

According to the DS, mechanistic data that could dismiss the relevance of these tumours for humans are not available. Therefore, these tumours are considered to be treatment-related and provide limited evidence of carcinogenicity. Classification as a Category 2 carcinogen was therefore proposed by the DS, without specifying a particular route of exposure.

Comments received during public consultation

Three MSCAs supported the classification proposal from the DS. One industry representative however opposed to the proposed classification as Carc. 2 with the following arguments:

- the effects are observed at doses exceeding the MTD (more than 10% reduction in body weight gain) in two mice strains and as a consequence, they should not be considered relevant for classification;
- there is no evidence of pre-neoplastic lesions, all tumours were benign, with no progression to carcinoma;
- type II bronchio-alveolar adenomas seen in mice are not generally seen in man;
- pirimicarb was demonstrated to be non-genotoxic;
- there are limited control data for ovarian tumour type occurring in the study in Alderley Park mice;
- the type of ovarian tumour that occurred in the mouse study is not commonly observed as a treatment-associated ovarian lesion in rodent carcinogenicity studies.

Assessment and comparison with the classification criteria

Three carcinogenicity studies, a one 90-day oral study in Alderley Park (Sprague Dawley-derived) rats (Tinston 1992), and two mouse studies – an 80-week oral study in C57 black mice (Rattray, 1998) and a lifetime feeding study in Alderley Park Swiss-derived mice (Sotheran *et al*., 1980), considered by the DS to be of sufficient quality for inclusion in the classification and labelling analysis, were considered by RAC. The findings of the other three studies in rodents are briefly presented for completeness, but they are deemed unreliable due to poor study design and an outbreak of respiratory disease that led to increased mortality and treatment with antibiotics.

In the rat study (see Tables 1 and Table 4 in "Supplemental information"), a dose-related increase in the incidence of astrocytoma in males and uterine stromal cell polyp in females was observed. Also, an increased incidence of meningioma in the mid dose males and top dose females, and uterine stromal cell sarcoma and mammary gland fibroadenoma in top dose females, was found. RAC supports the DS's and DAR rapporteur's conclusion that these tumours are not clearly treatment-related because they were within the historical control range (e.g. brain astrocytoma, uterine stromal cell polyp, uterine stromal cell sarcoma, mammary gland fibroadenoma, Table 5 in "Supplemental information") or did not follow a clear dose-response pattern (e.g. brain meningioma, mammary gland fibroadenoma). In addition, when interim kill data were included (Tables 1 and 4 in "Supplemental information"), only data for terminal kill and intercurrent deaths are presented, to be comparable with the historical control data that did not include an interim kill) no dose-response pattern was observed for astrocytoma incidence in males (0% in controls, 3% in low dose, 2% in mid dose and 3% in top dose males). Other tumours presented in Table 1 ("Supplemental information"), namely benign thymoma and adrenal gland adenoma, did not follow a dose-related pattern either or were present only at the top dose (adrenal gland adenoma in females).

In the reliable 80-day study in C57 black mice (Tables 2 and 4 in "Supplemental information") an increased incidence of lung adenomas in top dose females (700 ppm) was found, exceeding both concurrent and historical control values (3 fold higher than the upper value of the historical control range). The relevance of this finding was challenged by industry during public consultation.

1. Lung adenoma occurring at the dose level potentially exceeding the MTD
During public consultation, Industry argued that 700 ppm in mice is above the MTD due to a 23% decrease in total body weight gain compared to controls. The guidance on the application of the CLP criteria (version 4.0, Novembre 2013) states that in lifetime bioassays "...*the highest dose needs to induce minimal toxicity, such as characterised by an approximately 10% reduction in body weight gain (maximal tolerated dose, MTD dose)*". The MTD is the highest dose of the test agent during the bioassay that can be predicted "*not to alter the animal's normal longevity from effects other than carcinogenicity* (CLP guidance, version 4.0, November 2013)."

The following survival data and non-neoplastic effects were recorded in females dosed at 700 ppm:

- treatment did not affect mortality rate in any exposed group at the survival rates greater than 85% across all dose groups;
- a slight increase in the incidence of eye discharge and subcutaneous masses that was not related to adverse histopathological changes;
- an increase in relative liver weight (18%) not associated with pathological microscopic changes;
- changes in red blood cells parameters (<10% difference from control values in RBC count, MCV and MCHC) that were not indicative of anaemia (no effect on haemoglobin level);
- increased platelet count by 30% compared to controls; however, platelet count has a wide range of values in healthy animals (e.g. in adult male C57BL/6 mice it ranged from 620-1200 x 10^3/µL; Barrios *et al*., 2009), and adverse effects related to thrombocytosis (i.e. thrombotic events) were not reported;
- increased incidence of lymphoid proliferation in the lungs and of spleen pigmentation; however, pigmentation of the spleen (and of some other organs) and lymphoid accumulation in lungs, liver and lacrimal glands, are common non-neoplastic findings in the black mouse (Brayton, 2009).

The RAC does not consider the changes listed above as indicators of severe toxicity. Nevertheless, in the event that the top dose would be considered to be above the MTD, classification remains an option according to the CLP guidance: "*If a test compound is only found to be carcinogenic at the highest dose(s) used in a lifetime bioassay, and the characteristics associated with doses exceeding the MTD as outlined above are present, this could be an indication of a confounding effect of excessive toxicity. This may support a classification of the test compound in Category 2 or no classification*."

2. The relevance of type II pneumocyte-arising tumours for humans
Although rare, benign and malignant tumours that arise from type II pneumocytes occur in humans: alveolar adenoma, a very rare benign tumour (WHO histological classification of tumours of the lung), and bronchioloalveolar carcinoma represent less than 4% of all lung tumours (Read *et al*., 2004). Bronchioloalveolar carcinoma is a type of lung adenocarcinoma, predominantly of non-mucinous form composed primarily of type II pneumocytes or Clara cells (Lonardo, 2013). Type II pneumocytes are crucial for repair of the injured alveolus since they differentiate into alveolar epithelial type I cells (Wang *et al*., 2007). Type II cells possess proliferative potential so they could accumulate mutations that initiate tumour development (Lin *et al*., 2012). In the open literature it is stated that "*Spontaneous lung tumours in mice are similar in morphology, histopathology, and molecular characteristics to human adenocarcinomas. Mouse models for lung cancer can thus serve as a valuable tool not only for understanding the basic lung tumor biology but also for the development and validation of new tumour intervention strategies as well as for the identification of markers for early diagnosis*" (Meuwissen and Berns, 2005). Therefore, in the opinion of RAC, also in agreement with the DS proposal, human relevance of lung adenomas in mice, which are considered to arise from type II pneumocytes, could not be excluded. In addition, no mechanistic data were presented that could dismiss the relevance of these tumours for humans.

3. Increased incidence of lung adenomas observed only in females
In the Rattray study conducted in C57BL mice, top dose females received an almost 40% higher dose than top dose males (130.3 mg/kg bw/d *vs.* 93.7 mg/kg bw/d), although it is questionable whether this difference could explain the two times higher lung adenoma incidence in females compared to males. Nevertheless, according to the CLP guidance: "*There may be cases where tumours are only observed in one sex... A default position is that such tumours are still evidence of carcinogenicity and should be evaluated in light of the total tumorigenic response...*". In humans, alveolar adenoma and bronchioloalveolar carcinoma has a slight female predominance (WHO histological classification of tumours of the lung; Zell *et al.*, 2005), and the incidence for all adenocarcinomas was recorded to be more than two times higher in women than in men (Radzikowska *et al*., 2004).

Based on these arguments, RAC concludes that lung adenoma in female mice are treatment-related and relevant for pirimicarb classification. In addition, a single incidence of benign keratinising squamous epithelioma in top dose females is considered to be supportive of a treatment-related effect in the lungs, since this type of lung tumour rarely occurs spontaneously in mice or rats (Dixon *et al.,* 2008). In the lifetime study conducted in Alderley Park Swiss derived mice (Tables 3 and 4 in "Supplemental information") an increased incidence of lung adenoma, liver tumours, mammary gland tumour and ovary tumour was observed in exposed animals.

Pirimicarb treatment in males did not affect survival rate in exposed groups, which was rather low at all dose levels (21.7-28.8% in exposed groups, 33.3% and 26.6% in controls). In the top dose males (1600 ppm), besides decreased body weight gain (by 24%), non-neoplastic adverse effects were not reported. On the other hand, the highest dose significantly decreased survival rate in females (11.4% compared to 30.4% and 21.9% in two control groups), as well as body weight gain (for 41%). Therefore, this dose is considered to exceed the MTD in female mice.

Lung adenoma incidence was increased in males at the highest dose and in females at the highest and mid dose. However, spontaneous lung adenoma incidence in this mouse strain is high and variable (up to 18.3% in males and 13.3% in females according to historical control range; 15% and 6.8% in two contemporary female control groups).

The increased incidence of benign liver tumours in females and malignant liver tumours in males was above the historical control range, but did not follow a dose-related pattern. An increased incidence of benign liver tumours in males (26.3%) occurred at the top dose, and was not markedly above the historical control range (8-21.7%, median 14.4%). An increased incidence of malignant liver tumours in females occurred only at the highest dose that exceeded the MTD, and was slightly above (for 0.2%) the upper limit of the historical control range (0-8.3%, median 3.3%).

Mammary gland adenocarcinoma occurred at an incidence exceeding the historical control range only at the top dose, that was above the MTD.

Ovarian papillary cystadenoma (benign epithelial tumour) occurred at an incidence above the historical control range in mid and top dose females, without a clear dose-response pattern (5.5% and 5.4% at mid and high dose, respectively).

This study was however not considered reliable by RAC (in agreement with the DS) due to very low survival rates in all dose groups, including a less than 25% survival rate in control females, and 26.7% and 23.3% survival rates in control and low dose males, respectively. In addition, tumour incidence data were not adjusted for survival (namely, since animals that died early are expected to have a lower risk of tumour than animals that died later, the absence of dose-response cannot be reliably confirmed) and relevant historical control data were rather limited (3 studies with 2 control groups per study). In light of these issues, together with high and variable spontaneous lung adenoma incidence in this mouse strain, RAC considers the increased incidence of tumours in this study only as a supportive evidence for carcinogenic potential of pirimicarb.

According to the CLP criteria, a substance should be classified in Category 1B if "*a causal relationship has been established between the agent and an increased incidence of malignant neoplasms, or of a combination of benign and malignant neoplasms in at least two species or in two independent studies in one species*". Substances may also be classified in Category 1B according to CLP if they produce an "*increased incidence of tumours in both sexes of a single species in a well-conducted study or if the substance leads to an unusual degree of malignant neoplasms in one species and sex*". For pirimicarb the carcinogenicity findings are not considered to fulfil these conditions; RAC is of the opinion that the pirimicarb data do not justify a classification in CLP Category 1B.

If there is limited evidence of carcinogenicity in animal studies, classification as a Category 2 carcinogen or even no classification is possible. Following the weight of evidence approach, classification in Category 2 for pirimicarb is proposed by RAC based on limited evidence of carcinogenicity in animal studies according to CLP criteria:

- "*the evidence of carcinogenicity is restricted to a single experiment*": only the C57 black mouse study is considered to substantially indicate treatment-related tumourigenesis;
- "*the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential*": increase in benign lung tumour incidence is considered as relevant for classification.

Therefore, RAC agrees with the DS proposal to classify pirimicarb as a carcinogen of Category 2 (Carc. 2), with the hazard statement H351: Suspected of causing cancer (without specifying a particular route of exposure), based on the increased incidence of lung adenomas in female C57 black mice and the absence of mechanistic data that could dismiss the relevance of these lung adenomas for humans.

RAC considers that a single incidence of benign keratinising squamous epithelioma in C57 black mice females at the highest dose is considered to be supportive of a treatment-related effect in the lungs. Also, an increased incidence of lung adenomas, liver tumours and ovarian papillary cystadenoma in Alderley Park Swiss derived mice in a study with low survival rates without survival-adjustment for tumour incidence and in a strain with higher and more variable spontaneous incidence of lung tumours than C57 black mouse strain, are considered as supportive evidence for the carcinogenic potential of pirimicarb.

RAC evaluation of environmental hazards

Summary of the Dossier submitter's proposal

Pirimicarb is currently classified in annex VI of CLP as Aquatic Acute 1 and Aquatic Chronic 1. The DS proposed to add M-factors and classify the substance accordingly as Aquatic Acute 1 (M=10) and Aquatic Chronic 1 (M=100).

Degradation

A hydrolysis study conducted according to US EPA guideline subdivision N 161-1 was run at pH 5, 7 and 9 at 25°C over a period of 32 days in the dark. The study indicates that pirimicarb is hydrolytically stable since less than 5% hydrolysis was observed under the environmental conditions used in the study.

The studies of aqueous photolysis showed that pirimicarb undergoes photodegradation in water. In the first study, carried out according to SETAC and US EPA 161-2 guidelines at pH 5 and 7 using Xenon lamp at 25°C for periods equivalent to 31 hours of summer sunlight at 30°C, the experimental first order half-lives were calculated as 2.6 hours at pH 5 and 1.9 hours at pH 7. In the second study, following SETAC guidelines, pirimicarb was irradiated at 315 nm in purified water for 8 hours at 20°C and unknown pH. The estimated half-lives, determined by the Frank and Klopffer simulation model at irradation conditions equivalent to central Europe (Frank and Klopffer, 1988, 1989) for the top 0-30 cm of a pure water column were 12 hours in June and 264 hours in December. In the third study, performed according to SETAC and US EPA 161-2 guidelines subdivision at 20 °C and unknown pH, test samples were irradiated at 313 nm until 2-12% of pirimarb was degraded. Using the Frank and Klopffer simulation model,

the estimated half-lives for the top 0-30 cm of a pure water column in central Europe were 16 hours in summer and 290 hours in winter.

No data on ready biodegradability were available.

A water/sediment simulation study, carried out according to SETAC and German BBA guidelines, using ^{14}C-pirimidinyl radiolabelled pirimicarb, was run over 100 days in the dark at 20±2 °C using two pond systems. The sediment/water ratio (1:3.6) in the experiment was slightly higher than the range specified in the guidelines (1:4 to 1:10).

In both systems, pirimicarb concentrations in water decreased during the experiment with an increase in pirimicarb concentrations in sediment and pirimicarb degradants (R034836, R034885 and R031805[1]). No degradant was observed at ≥ 10% of applied radioactivity (AR). Up to 1.5% of AR was completely mineralized to carbon dioxide after 100 days.

For pirimicarb, the half-lives in water were 55 and 36 days while reliable DT_{50} in sediment could not be determined as concentrations of pirimicarb were still increasing in sediment at the end of the study. For the whole systems, half-lives of 194 and 166 days were calculated by the study authors from the data. Different values for whole systems half-lives (185 and 156) are included in the EFSA pesticide peer review conclusion on pirimicarb (2005), but their derivation is unclear.

Aerobic and anaerobic degradation in soil studies, according to US EPA 162-1 and 162-3 guidelines, were carried out at 20°C in the dark using soils treated with ^{14}C-pirimidinyl radiolabelled pirimicarb at a rate equivalent to 1.49 kg a.s./ha. Treated samples were removed at intervals (up to 372 days) during the incubation and analysed for parent and major metabolites, $^{14}CO_2$ and any other volatilised radioactivity were trapped and quantified. Limited mineralization with a maximum of 3% AR was observed at day 112.

The DS concluded that pirimicarb is not considered as rapidly degradable.

Bioaccumulation

Pirimicarb has a log Kow of 1.7 (20°C , pH 7.1). A bioaccumulation study was not conducted because the bioaccumulation potential of pirimicarb is low.

Aquatic toxicity

The DS provided aquatic toxicity data for each trophic level on pirimicarb and on the most relevant metabolites. However, only information on pirimicarb was considered relevant, as it is considered more toxic than its degradants. Further, pirimicarb is not rapidly degradable and exposure to its degradants is likely to be minimal.

Regarding short-term toxicity, two tests with fishes (*Oncorhynchus mykiss* and *Pimephales promelas*), two with aquatic invertebrates *(Daphnia magna)* and one test with algae (*Pseudokirchneriella subcapitata*) were provided. Regarding long-term toxicity, there are three available tests, two with fishes (*Oncorhynchus mykiss* and *Pimephales promelas*) and one with aquatic invertebrates *(Daphnia magna)*.

Invertebrates are known as the most acutely and chronically sensitive trophic level. Between the acute toxicity tests, the study on *Daphnia magna* (according to US EPA 72-2 and OECD TG 202, under GLP) is considered as the decisive study, with a static 48-h EC_{50} =0.017 mg/L (nominal concentration). This result is supported by a second study on *Daphnia magna*, not perfomed according to GLP and without following a specific test guideline, with a 48-h EC_{50} value (nominal concentration) between 0.011 and 0.033 mg/L.

[1] R034836: 5,6-dimethyl-2-(methylamino) pyrimidin-4yl dimethylcarbamate
R034885: 5,6-dimethyl-2-(methylformamido) pyrimidin-4yl dimethylcarbamate
R031805: 2-dimethylamino-5,6-dimethylpyrimidin-4ol

The long-term aquatic key study is the *Daphnia magna* study (according to OECD 202, part II (1984), GLP). The results are reported with a semi-static 21-d NOEC =0.0009 mg/L based on length, and =0.0017 mg/L based on reproduction.

The following table summarises the reported studies on aquatic toxicity for pirimicarb. The key values used for the purpose of classification are shown in bold.

Test Guideline	**Purity**	**Species**	**Remarks**	**Endpoint**	**Toxicity values in mg/L**	**Ref.**
Short-term toxicity to fish						
US EPA 72-1 and OECD TG 203	98.9%	Rainbow trout (*Oncorhynchus mykiss*)	Static Mean measured conc 100-103%, therefore based on nominals	96-h LC_{50}	79	Kent *et al.*, 1998a and 1998b
US EPA 72-1	98.9%	Fathead minnow (*Pimephales promelas*)	Static Based on highest nominal test conc	96-h LC_{50}	>100	Magor *et al.*, 1998

Long-term toxicity to fish						
OECD TG 204	96-98 %	Rainbow trout (*Oncorhynchus mykiss*)	Semi-static Based on mean measured test conc	28-d NOEC	<18	Tapp *et al.*, 1989
EPA 72-4	97.5 %	Fathead minnow (*Pimephales promelas*)	Flow-through Based on mean measured test conc	36-d NOEC based on growth	10	Kent *et al.*, 1996
Short-term toxicity to aquatic invertebrates						
US EPA 72-2 and OECD TG 202	97.5 %	*Daphnia magna*	Static Mean measured 100-109%, therefore based on Nominal conc	48-h EC_{50}	**0.017**	Kent & Shillabeer, 1996a and 1996b
Not specified	99 %	*Daphnia magna*	Static Nominal conc	48-h EC_{50}	0.011-0.033	Hamer, 1995
Long-term toxicity to aquatic invertebrates						
OECD TG 202, part II (1984)	96.0 %	*Daphnia magna*	Semi-static Nominal conc	21-d NOEC Length 21-d NOEC Reproduction	**0.0009** 0.0017	Thompson *et al.*, 1989
Toxicity to Algae						
OECD TG 201	98.5%	Green algae (*Pseudokirchneriella subcapitata*)	Static Based on mean measured test Measured conc	24-96-h E_rC_{50} 24-96-h NOE_rC	180 50	Thompson, 1985

Comments received during public consultation

Four MSCAs submitted comments during public consultation supporting the proposed environmental classification. In particular, two MSCAs underlined the need to describe those key studies on which the classification is based, in a more detailed way. One MSCA suggested just an addition regarding additional data for acute fish toxicity which however does not change the proposed classification. The DS answered these comments in the RCOM stating that there is sufficient information in the CLH report to allow a decision on the environmental classification.

Assessment and comparison with the classification criteria

Degradation

RAC agrees with the DS proposal that pirimicarb should be considered as not rapidly degradable, based on the fact that less than 70% of pirimicarb degraded within 28 days in the hydrolysis study, no ready biodegradability study is available and less than 70% of the substance is not ultimately degraded in the water/sediment study. Although the studies of aqueous photolysis suggest that pirimicarb undergoes photodegradation, the actual degree of photodegradation in the aquatic environment is uncertain and not relevant for classification purposes.

Bioaccumulation

Pirimicarb has a measured log Kow of 1.7 (20 °C, pH 7.1). This log Kow is below the trigger of log kow = 4. Therefore RAC agrees with the conclusion of the DS that pirimicarb has no significant bioaccumulation potential.

Aquatic toxicity

Acute aquatic hazard

Acute toxicity data are available for all three trophic levels. Invertebrates are the most sensitive taxonomic group. The lowest reliable short-term aquatic toxicity result for *Daphnia magna* is 48-h EC_{50} = 0.017 mg/L (nominal concentration).

Chronic aquatic hazard

Long-term aquatic toxicity data are available for all three trophic levels. The lowest value is for invertebrate species *Daphnia magna*, with a 21-d NOEC = 0.0009 mg/L (nominal concentration).

Pirimicarb is considered not rapidly degradable and does not fulfil the criteria for bioaccumulation.

The lowest available result obtained for pirimicarb in a short-term test is EC_{50} value of 0.017 mg/L in *Daphnia magna*. In agreement with the DS proposal, RAC concludes that pirimicarb therefore fulfils the criteria for classification as **Aquatic Acute 1** with an **M-factor=10**, because the value is in the range: 0.01 mg/L < $L(E)C_{50}$ ≤ 0.1 mg/L.

In addition, the lowest available result from a long-term test obtained for pirimicarb is a NOEC value of 0.0009 mg/L in *Daphnia magna*. Pirimicarb therefore also fulfils the criteria for classification as **Aquatic Chronic 1** with an **M-factor=100**, because the value is in the range: 0.0001 mg/L < NOEC ⩽ 0.001 mg/L and the substance is not rapidly degradable.

References

Barrios M, Rodríguez-Acosta A, Gil A, Salazar AM, Taylor P, Sánchez EE, Arocha-Piñango CL, Guerrero B. (2009). Comparative hemostatic parameters in BALB/c, C57BL/6 and C3H/He mice. Thromb. Res. 124(3):338-43

Beamer WG, PC, Hoppe PC, Whitten WK. (1985). Spontaneous malignant granulosa cell tumors in ovaries of young SWR mice. Cancer Res. 45:5575-81

Brayton C. (2009). Spontaneous Diseases in Commonly Used Mouse Strains/Stocks. Outline Rev. Johns Hopkins University, Baltimore, MD.

Dixon D, Herbert RA, Kissling GE, Brix AE, Miller RA, Maronpot RR. (2008). Summary of chemically induced pulmonary lesions in the National Toxicology Program (NTP) toxicology and carcinogenesis studies. Toxicol Pathol. 36(3):428-39

Frank R. and Klopffer W. (1989). A convenient model and program for the assessment of abiotic degradation of chemicals in natural waters. Ecotoxicol. Environ. Saf. 17, 323-332.

Frank R. and Klopffer W. (1988). Spectral solar photon irradiance in Central Europe and the adjacent North Sea. Chemosphere 17:985-994.

Lin C, Song H, Huang C, Yao E, R Gacayan, Xu SM, Chuang PT. (2012). Alveolar Type II Cells Possess the Capability of Initiating Lung Tumor Development. PLoS One. 7(12): e53817

Lonardo F (Reviewer). (2013). Adenocarcinoma-classification. Revised: 11 January 2013. PathologyOutlines.com, Inc.

Maibach HI. (2001). (Ed.) Toxicology of Skin. Taylor & Francis.

Meuwissen R, Berns A. (2005). Mouse models for human lung cancer. Genes Dev. 19(6):643-64
Poteracki J, Walsh KM. (1998). Spontaneous neoplasms in control Wistar rats: a comparison of reviews. Toxicol Sci. 45(1):1-8

Radzikowska E, Głaz P, Roszkowski K. (2002). Lung cancer in women: age, smoking, histology, performance status, stage, initial treatment and survival. Population-based study of 20 561 cases. Ann Oncol. 13(7):1087-93

Read WL, Page NC, Tierney RM, Piccirillo JF, Govindan R. (2004). The epidemiology of bronchioloalveolar carcinoma over the past two decades: analysis of the SEER database. Lung Cancer 45(2): 137–42

Wang D, Haviland DL, Burns AR, Zsigmond E, Wetsel RA. (2007). A pure population of lung alveolar epithelial type II cells derived from human embryonic stem cells. PNAS 104:4449-54

WHO histological classification of tumours of the lung. (2004). In: Travis WD et al. (Eds.) Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. IARCPress Lyon, 2004.

Zell JA, Ou SH, Ziogas A, Anton-Culver H. (2005). Epidemiology of bronchioloalveolar carcinoma: improvement in survival after release of the 1999 WHO classification of lung tumors. J Clin Oncol. 23(33):8396-405.

ANNEXES:

Annex 1 Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in RAC boxes.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and rapporteurs' comments (excl. confidential information).