Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling at Community level of

Nitrobenzene

ECHA/RAC/CLH-O-0000002350-87-01/F

Adopted

3 February 2012

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

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

Substance Name: Nitrobenzene

EC Number.: 202-716-0

CAS Number.: 98-95-3

The proposal was submitted by ***Germany***
and received by RAC on **17 January 2011**

The harmonised classification proposed by the Dossier submitter

	CLP Regulation (EC) No 1272/2008	Directive 67/548/EEC
Current entry in Annex VI CLP Regulation	Carc. 2 H351 Repr. 2 H361f*** Acute Tox. 3* H331 Acute Tox. 3* H311 Acute Tox. 3* H301 STOT RE 1 H372** Aquatic Chronic 2 H411	Carc. Cat. 3; R40 Repr. Cat. 3; R62 T; R23/24/25-48/23/24 N; R51-53
Current proposal for consideration by RAC	<u>Nitrobenzene containing <0.1% benzene:</u> Carc. 2 H351 Repr. 2 H361f Lact. H362 Acute Tox. 3 H331 Acute Tox. 3 H311 Acute Tox. 3 H301 Asp. Tox 1 H304 STOT RE 1 H372 Aquatic Chronic 3 H412 <u>Nitrobenzene containing ≥0.1% benzene:</u> Carc. 1A H350 Muta. 1B H340 Repr. 2 H361f	<u>Nitrobenzene containing <0.1% benzene:</u> Carc. Cat. 3; R40 Repr.Cat.3, R64 T; R23/24/25-48/23/24/25-65 R52-53 <u>Nitrobenzene containing ≥0.1% benzene:</u> Carc.Cat.1, R45 Muta.Cat.2, R46

	Lact. H362 Acute Tox. 3 H331 Acute Tox. 3 H311 Acute Tox. 3 H301 STOT RE 1 H372 Asp. Tox 1 H304 Aquatic Chronic 3 H412	Repr.Cat.3, R64 T; R23/24/25-48/23/24/25-65 R52-53
Resulting harmonised classification (future entry in Annex VI of CLP Regulation)	<u>Nitrobenzene containing <0.1% benzene:</u> Carc. 2 H351 Repr. 2 H361f Lact. H362 Acute Tox. 3 H331 Acute Tox. 3 H311 Acute Tox. 3 H301 STOT RE 1 H372 Asp. Tox 1 H304 Aquatic Chronic 3 H412 <u>Nitrobenzene containing ≥0.1% benzene:</u> Carc. 1A H350 Muta. 1B H340 Repr. 2 H361f Lact. H362 Acute Tox. 3 H331 Acute Tox. 3 H311 Acute Tox. 3 H301 STOT RE 1 H372 Asp. Tox 1 H304 Aquatic Chronic 3 H412	<u>Nitrobenzene containing <0.1% benzene:</u> Carc.Cat.3, R40 Repr.Cat.3, R62, R64 T; R23/24/25-48/23/24/25-65 R52-53 <u>Nitrobenzene containing ≥0.1% benzene:</u> Carc.Cat.1, R45 Muta.Cat.2, R46 Repr.Cat.3, R62, R64 T; R23/24/25-48/23/24/25-65 R52-53

PROCESS FOR ADOPTION OF THE OPINION

Germany 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/consultations/harmonised_cl/harmon_cl_prev_cons_en.asp*** on 17 January 2011. Parties concerned and MSCAs were invited to submit comments and contributions by 03 March 2011.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: ***Boguslaw Baranski***

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

The RAC opinion on the proposed harmonised classification and labelling has been reached on ***3 February 2012*** in accordance with Article 37(4) of the CLP Regulation, giving parties concerned the opportunity to comment. Comments received are compiled in Annex 2.

The RAC Opinion was adopted by ***consensus***.

OPINION OF RAC

The RAC adopted the opinion that nitrobenzene should be classified and labelled as follows:

Classification & Labelling in accordance with the CLP Regulation for Nitrobenzene:

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)		
609-003-00-7	Nitrobenzene	202-716-0	98-95-3	Carc. 2. Repr. 1B Acute Tox. 3 Acute Tox. 3 Acute Tox. 3 STOT RE 1 (blood) Aquatic Chronic 3	H351 H360F H301 H331 H311 H372 H412	GHS06 GHS08 Dgr	H351 H360F H301 H331 H311 H372 H412			

Classification & Labelling in accordance with Directive 67/548/EEC for Nitrobenzene:

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
609-003-00-7	Nitrobenzene	202-716-0	98-95-3	Carc. Cat. 3; R40 Repr. Cat. 2; R60 T: R23/24/25 T: R48/23/24/25 R52/53	T, R:23/24/25-48/23/24/25-40-60-52/53 S: 1/2-27-36/37-45-46-53		

SCIENTIFIC GROUNDS FOR THE OPINION

The opinion relates only to all those hazard classes that have been reviewed in the proposal for harmonised classification and labelling, as submitted by *Germany*.

Health hazards

Acute Toxicity
Acute oral toxicity

Median lethal doses after oral administration of nitrobenzene to female and male rats in four animal studies listed in 5.2.1.2. of the Background document were in a range from >450 to 732 mg/kg/ bw, thus they were according to DSD classification within the dose range of 200 - 2000mg/kg/bw for substances classified as harmful and assigned the symbol 'Xn" and a risk phrase R22 Harmful if swallowed. These oral LD50 for rats are also within CLP regulation criteria for the acute oral toxicity hazard category 4 equal 300 to 2000mg/kg/bw which would allow to classify nitrobenzene to Acute Tox. 4 - H302.

The lethal oral dose of nitrobenzene to cats was reported to be 2400 mg/kg bw and minimal lethal dose in dogs was stated to be 750 – 1000 mg/kg of body weight by von Oettingen in 1941 (EHC 230, 2003).

Based on a case-study of Harrison (1977) describing , after intensive medical treatment, recovery of a man, who ingested nitrobenzene in an approximate dose of 400mg/kg it might be assumed that this dose could be lethal to man without medical treatment. In another case a man has survived, after medical treatment, oral intake of 200 ml (240g) of nitrobenzene corresponding roughly to 240g/70kg = 3400mg/kg. In two other case studies (Myslak et al. 1971; Kumar et al. 1990) patients survived oral intake of 50ml and 30-40ml of nitrobenzene, which is equal to 60g and 36-48g of nitrobenzene. These data may allow to assume that the lethal-without treatment dose of nitrobenzene could be equal to 60 000mg/70kg = 857mg/kg and 42 000mg/70kg = 600mg/kg.
The lowest dose of nitrobenzene reported to induce serious intoxication of a woman was approximately 230mg/kg (Parkes and Neil,1953). Having in mind the known interspecies variation in sensitivity to toxicity of chemicals, it may be reasonably assumed that nitrobenzene even at doses lower than 230mg/kg (Parkes and Neil, 1953) may be seriously toxic to humans. Thus the doses inducing serious toxicity in humans may be lower than a range of median lethal doses for rats used as criteria for classification of acute toxicity.

In addition it is known that humans are more sensitive than rats to MetHb- formation under influence of chemical substances, e.g. aniline, as described in the Background Document. The lowest oral dose of aniline significantly increasing level of methemoglobin (from 1.2% to 2.5%) in human volunteers receiving this substance once a day for three consecutive days was 25 mg/person, which may be converted to 25mg/70kg= 0.36mg/kg (Jenkins et al., 1972 quoted from Aniline EU Risk Assessment Report, ECB, 2004) . The lowest dose of aniline causing a slight increase in Met-Hb in rats (3.3% versus 2.4% in controls) amounted to 20mg/kg (Jenkins at al., 1972 from ECB, 2004). Thus humans are 56 times (20mg/kg/0.36mg/kg) more sensitive to Met-Hb formation than rats. This ratio of sensitivities to Met-Hb formation between humans and rats is much higher than 10 usually taken as a default value for interspecies differences in susceptibility to toxic action of chemicals (guidance). Higher susceptibility of humans is likely to be a consequence of the interspecies differences in the activity of methaemoglobin reductase, which reduces methaemoglobin to haemoglobin. The activity of this enzyme is five and ten times higher in rat and mouse erythrocytes, respectively than in human erythrocytes (Smith, 1986 quoted from ECB, 2004).

Taking into account that formation of Met-Hb, in response to a single exposure to nitrobenzene, may cause secondary toxic effects in internal organs such as spleen, liver, kidney, brain and lungs, the high difference between humans and rats in susceptibility to induction of Met-Hb should be taken into consideration in the hazard classification.

Therefore, in the opinion of RAC the classification derived solely on animal data - Xn with a risk phrase R 22 Harmful if swallowed (DSD) and Acute Tox. 4 with hazard statement H302 Harmful if swallowed – is not relevant for humans because of the higher sensitivity of humans to Met-Hb forming action of nitrobenzene, thus acute oral toxicity of nitrobenzene should by classified T: R25 Toxic if swallowed (DSD) and Acute Tox. 3, H301 - Toxic if swallowed.

This classification is in agreement with the existing classification, a proposal of Dossier Submitter, opinion of TC C&L and opinions of some MSCAs expressed during public consultation.

Acute inhalation toxicity

The case-study provided by Henderson and Haggard (1943) indicate that one hour exposure of humans to nitrobenzene in the concentration ca. 1mg/l, which is slightly below the saturated vapour concentration (SVC) of nitrobenzene equal to 1.014 mg/l at 20^{o}C did not result in a serious alteration of health, which most probably means that observed symptoms did not require medical treatment and were not interpreted as a serious threat to health.

The saturated vapour concentration at 20°C for nitrobenzene is 1.014 mg/l, however at 25°C it may be as high as 1.93 mg/l . The data presented in section 5.2.2.2 of Background document indicate that LC_{50} for rats exposed for 3 and 7 hours hour to saturated vapour concentration (SVC) of nitrobenzene would be higher than 1.5 mg/l, and most probably higher than 3mg/l (BASF AG, 1977). Therefore based on these data it would be rather difficult to state that acute inhalation toxicity of vapour of nitrobenzene meets the classification criteria for T, R23 within DSD being for gases and vapours $0.5 < LC_{50} \leq 2$mg/l/4hr, or CLP criteria for Acute Tox. 2 being $0.5 < LC_{50} \leq 2$mg/l/4hr because of lack of mortality in rats in conditions corresponding to upper limit of a LD_{50} range defined in this criterion.
Even after large extension of time of inhalation exposure to 8 hour at saturated vapour concentration (SVC) at 23.1°C none of 6 rats died (Hoechst AG, 1977). None out 12 rats died after 7-hour exposure to SVC of nitrobenzene at 20°C, B Hoechst AG, 1981).

According to Guidance on the Application of Regulation (EC) No 1272/2008 (Annex I: 3.1.2.3. "Specific considerations for classification of substances as acutely toxic by the inhalation route", page 197) an LC_{50} well below the SVC will be considered for classification according to the criteria for vapours; whereas an LC_{50} close to or above the SVC will be considered for classification according to the criteria for mists
The data of DuPont report (1981) indicate that LC_{50} for rats of a mixture of mist and vapour of nitrobenzene equals 2.847 mg/l which is within a range of $1.0 < LC_{50} \leq 5$ mg/l/4hr which is a criterion for category Harmful "Xn" and risk phrase R20 within DSD system as well as criterion for Acute Tox. 4 and with hazard statement H332 within CLP system. The results of other animal studies on acute inhalation toxicity also support such a classification.

Taking into account that formation of Met-Hb, in response to a single exposure to nitrobenzene, may cause secondary toxic effects in internal organs such as spleen, liver, kidney, brain and lungs, the high difference between humans and rats in susceptibility to induction of Met-Hb should be taken into consideration in hazard classification.

Therefore, in the opinion of RAC the classification derived solely on animal data - Xn with a risk phrase R 20 (DSD) and Acute Tox. 4 with hazard statement H332 Harmful if inhaled – is not relevant for humans because of the higher sensitivity of humans to Met-Hb forming action of nitrobenzene, thus acute oral toxicity of nitrobenzene should by classified T: R23 Toxic by inhalation (DSD) and Acute Tox. 3, H331 Toxic if inhaled.

This classification is in agreement with the existing classification, a proposal of Dossier Submitter, opinion of TC C&L and opinions some MSCAs expressed during public consultation.

Acute dermal toxicity

The case reports described in background document indicate an ability of nitrobenzene to penetrate through undamaged human skin, even from diluted solutions, leading to formation of methemoglobin and visible cyanosis which somehow act as a warning signal leading to cessation of exposure. In all cases the induced symptoms disappeared in few days without medical treatment, except in one case, after cessation of exposure and no permanent damage was reported in the acutely intoxicated children after recovery.

The reported dermal LD_{50} for rats equal to 2100mg/kg and to rabbits amount to 301 mg/kg and to 760 mg/kg. The lowest reported LD_{50} equal 301mg/kg falls into a range of 50 – 400mg/kg, which is according to Directive 67/548/EEC a criterion of category Toxic "T" with risk phrase R 24 - toxic in contact with skin

However, the criteria for acute dermal toxicity according to CLP regulation are different. Taking only into account study on rats nitrobenzene could not be classified to acute dermal toxicity since dermal LD_{50} for rats (2100mg/kg) is outside classification range for category Acute Tox. 4 equal 1000 -2000 mg/kg in CLP Regulation, what demonstrate the rats are not appropriate model for assessment acute dermal toxicity for humans. Based on the study on rabbits nitrobenzene would be classified into category Acute Tox. 3, H311 since both LD_{50} for rabbits (301 mg/kg and 760 mg/kg) are within a range of 200 – 1000 mg/kg. Taking as basis results obtained in more sensitive species the classification for dermal toxicity Acute Tox 3 with a hazard statement H311 is proposed which is in agreement with the proposal of the dossier submitter.

This classification is in agreement with the existing classification, and the proposal from the Dossier Submitter, the conclusions of TC C&L and comments from some MSCAs expressed during public consultation.

Skin and eye irritation

Nitrobenzene after application on the skin or instillation into eye of rabbit in appropriate test conditions did not produce effects meeting criteria set in the Directive 67/548/EEC or in CLP regulation for a substance considered irritating to skin or eyes, therefore, no classification is warranted as proposed by the dossier submitter.

Skin sensitization

The available studies on skin sensitization properties of nitrobenzene were not performed with methods described in Council Regulation (EC) No 440/2008 or equivalent, internationally recognized methods. The effects observed in these available studies for nitrobenzene are not sufficient to assess sensitization properties of nitrobenzene. No classification is therefore proposed following a proposal of the dossier submitter.

Respiratory sensitisation

No data are available

Germ cell mutagenicity

The results of the in vivo mutagenicity tests (BASF AG, 1996, Kligerman et al. 1983, Miralis et al. 1982) summarized in the background document provide evidence that nitrobenzene do not induce mutations in somatic cells. No mutagenicity was also observed in in vitro mutagenicity tests. Sporadic inconclusive results in some tests were due to methodological insufficiencies.
The properties of nitrobenzene do not warrant classification for mutagenicity either in DSD or in CLP classification system as proposed also by the dossier submitter and TC C&L (2007).

Carcinogenicity

There are no data on carcinogenicity of nitrobenzene in humans thus classification has to be based on results of animal studies. The long-term carcinogenicity study of nitrobenzene has been performed by one scientific centre (CITT,1993; Cattley et al. 1994) on male and female F-344 rats, male Cd rats exposed to nitrobenzene vapour at concentrations 0, 0.005, 0.025, 0.13 mg/L (0, 1, 5, 25 ppm) for 6h/d, 5d/w for 107 weeks and male and female B6C3F1 mice exposed to nitrobenzene vapour at concentrations 0, 0.005, 0.025, 0.13 and 0.26 mg/L (0, 1, 5, 25 and 50 ppm) for 6h/d, 5d/w for 107 weeks . The value of the study is reduced because some internal organs considered by the authors as nontarget tissue such as lungs, kidney, adrenals, prostate, testes, ovaries, uterus were not microscopically examined in all exposed animals, but were examined only in control and highest exposed group animals.

Mice. In male mice there was statistically significant increase in frequency of animals with benign lung adenoma and thyroid adenoma in the 0.13mg/L group, but not in frequency of lung or thyroid carcinoma. In females the frequencies of lung adenoma and carcinoma were not different form the controls. The frequency of lung adenoma and combined adenoma and carcinoma in control male and female mice were 13% and 11 %, while in the highest dose group they were more frequent 35% and 10%. There was increase in frequency of mammary gland carcinoma (8%) in female mice exposed at 0.26 mg/L, but female mice exposed at lower concentrations were not microscopically examined. Historical control values were not given. There was a relatively high frequency of hepatocellular adenoma and carcinoma in liver of control and exposed mice, apparently not treatment related, reaching 37 % and 33% in control and highest dosed males, respectively, and 14% in control female and 23% in highest dose females.

Rats. There was a statistically significant increase in frequency of animals with hepatocellular adenoma in liver in male F344 and CD rats (but not in female F344 rats) exposed at the highest concentration, however there were no increases in frequency of these adenomas in rats exposed at lower concentrations. There was also an increased frequency of animals with tubular adenoma in kidney in male F344 rats exposed at highest concentration of 0.13 mg/l, but not in other exposed F 344 females and male CD rats. There was not treatment related increase in hepatocellular carcinoma or in tubular carcinoma in male or female rats.

This evidence of carcinogenicity should be interpreted as limited because there was significant increase in frequency of benign neoplastic changes such as adenoma in lung and thyroid only in male mice, but not in female mice. Increase in mammary gland carcinoma in highest group of female mice could not be supported by the results in low exposed group because they were not microscopically examined. The location of benign tumours in rats was different than in mice. They were located only in liver of male F344 and CD rats, and in kidneys of F344 rats, but not in female F344 rats. So there is inconsistency in neoplastic responses between mice and rats and between females and males, which is lowering the strength of evidence.

Based on this limited evidence RAC is of the opinion that nitrobenzene should be classified as Carc. 2 – H351 Suspected of causing cancer (CLP) and Carc. Cat 3, R40 limited evidence for carcinogenicity (DSD). This opinion of RAC supports earlier proposal for classification of carcinogenicity of nitrobenzene by TC C&L (2007).

The same classification was proposed by the dossier submitter and was supported by several MSCA during public consultation

Reproductive Toxicity

Fertility

The evidence has been provided in the background document that the reduced male fertility and/or atrophy of spermatogenic epithelium, or degeneration of tubular epithelium in testes were observed at exposure levels inducing low increases of methemoglobin concentration in blood (well below 10%), but not high enough to result in significant hypoxia in peripheral tissue.

All studies of repeated toxicity and toxicity to reproduction carried out on rats and mice demonstrated that nitrobenzene causes the following adverse effects on spermatogenesis:

1. degeneration of seminiferous tubular epithelium and atrophy of seminiferous tubule of rats exposed by gavage for 28 days at the dose of 125 mg/kg (Shimo et al. 1994)

2. atrophy of seminiferous epithelium, hypospermatogenesis and presence of multinucleate giant cells in testes of male F344 rats exposed at the dose of 75 and 150 mg/kg to nitrobenzene for 90 days via gavage, and in testes of male B6C3F1 mice exposed at the dose of 150 and 300 mg/kg to nitrobenzene for 90 days via gavage (NTP 1983a cited from U.S. EPA (2009)

3. moderate to severe degeneration of tubular epithelial cells was noted in the testes of all F344 male rats exposed by inhalation to 0.26 mg/L (50 ppm) for 90 days . This consisted of a maturation arrest at the level of primary and secondary spermatocytes and was usually accompanied by interstitial edema and Leydig cell hyperplasia. An absence of mature sperm was noted in the epididymis of these animals, together with the presence of proteinacious material within the lumen of the ductus. (CIIT subchronic study, 1984/ Hamm, 1984.)

4. CD rats exposed by inhalation for 90 days at the highest concentration – 0.26 mg/L displayed a marked bilateral testicular atrophy in response to nitrobenzene, as indicated by a loss of seminiferous epithelium with only a few scattered spermatogonial cells present, interstitial cell hyperplasia, oedema, and the absence of mature sperm in the epididymal lumen. (CIIT subchronic study, 1984/ Hamm, 1984.)

5. bilateral atrophy of the testis (57% at the highest dose vs. 18% of controls) and bilateral hypospermia of the epididymis (54% at the highest dose vs. 13% of controls) was observed in CD male rats exposed for 2 years by inhalation to nitrobenzene at the highest concentration of 0.13mg/l as well as increased incidence of hypospermia in epididymis in male mice exposed for 2 years by inhalation at concentration of 0.26 mg/l (Cattley et al. (1994); CIIT (1993)

6. atrophy of seminiferous epithelium, hypospermatogenesis and presence of multinucleate giant cells in testes of male F344 rats exposed to nitrobenzene for 90 days via dermal exposure at doses of 400 and 800mg/kg and in testes of male B6C3F1 mice exposed by dermal route for 90 days at doses of 400 and 800 mg/kg to nitrobenzene (NTP 1983a cited from U.S. EPA (2009) (NTP,1983b study cited from US EPA, 2009).

7. atrophy of the seminiferous tubules, hyperplasia of Leydig cells, and loss of intraluminal sperm in the epididymides in male SD rats exposed for 40 - 54 days by gavage at doses of 60 or 100 mg/kg-day nitrobenzene in sesame oil (Mitsumori at al. 1994)

The alteration of fertility due to disturbances in spermatogenesis were confirmed in 2-generation reproductive toxicity study and other studies

1. reduced fertility index (number of pregnancies/number of females mated) SD rats in F0 and F1 generations and reduced gestation index (number of pregnancies with live litters/number of pregnancies) in a 2-generation study, in which rats were exposed by inhalation at concentration of 0.204mg/l 6hr/day, 5 days /week for two generations. These reductions were associated with atrophy of seminiferous epithelium in testes of F0 and F1 generations exposed at the highest concentration of 0.204mg/l (Dodd at al. 1987).

2. reduced fertility index of rats receiving 60mg/kg of nitrobenzene by gavage after 3 weeks of exposure. The value of fertility index was further dropping down with duration of exposure leading to infertility of male rats after 28 days of exposure. The fertility index due to oral nitrobenzene exposure was not affected until sperm count was depressed at or below 10%. (Kawashima et al. 1995)

The results of these studies reviewed in the background document provide sufficient evidence that nitrobenzene has a property of causing serious alterations of spermacytogenesis and spermiogenesis in two animal species: rats and mice; leading to reduced fertility and to infertility of male animals. Thus there is sufficient evidence providing a strong presumption that human exposure to the nitrobenzene may result in the same adverse effects on the basis of clear evidence in animal studies of impaired fertility. These toxic effects were occurring at dose levels which did not induce severe methemoglobinemia and they were not a secondary non-specific consequence of the other toxic effects.

Therefore RAC is of the opinion that there is sufficient evidence to classify nitrobenzene according to the CLP regulation for the reproductive toxicity category 1B Presumed human reproductive toxicant with hazard statement H360F (Repr. 1B - H360F) and according to Directive 548/67 to Repr. Cat 2: R60 – may impair fertility

The rationale for the RAC opinion is different from the rationale of dossier submitter and TC C&L (2007) proposing to classify nitrobenzene to Repr.Cat.3; R62 and Repr. 2; H 361f.

TC C&L has acknowledged that: *"Numerous studies with rats and mice revealed nitrobenzene to persistently adversely affect male reproductive organs (atrophy of the germ epithelium) and spermatogenesis independently from the route of administration (inhalation, oral, dermal)"* however it has decided to weaken this evidence based on the following recognitions:

- *"haematotoxicity is the predominating toxic effect after treatment with nitrobenzene and that these latter effects were also observed in the available reproduction toxicity studies with nitrobenzene.*
- *humans in comparison to the rat species are much more sensitive to the induction of methaemoglobinaemia and that* ***the rat as an experimental model rather may underestimate the significance of methaemoglobin-induced haematotoxicity of nitrobenzene****.*
- *as far as both haematological as well as reproduction parameters had been evaluated in the studies available with nitrobenzene, haematotoxicity was consistently induced at dose levels clearly below those inducing testes toxicity.*

Therefore, nitrobenzene is not considered to represent a specific reproductive toxicant".

RAC noted that reproductive toxicity of nitrobenzene is not related to its hematotoxicity as was assumed earlier. The increase in levels of methemoglobin up to 10% by exposure to aniline is not leading to a damage of spermatogenic epithelium, therefore the latter is not a secondary effects of increased level of methmoglobin. Such a conclusion may be derived from results of studies with repeated exposure of animals to aniline, which is, like nitrobenzene, a strong methemoglobin-forming substance. No alterations of spermatogenic epithelium were reported in rodents repeatedly exposed to aniline despite increased level of MetHb (SCTEE, 2003; ECB, 2004) Thus, the damage to spermatogenic epithelium and reduced fertility is a specific effect of nitrobenzene independent from its ability to induce MetHb and related hematotoxic effects.

The other incorrect argument for downgrading classification of reprotoxicity of nitrobenzene from Repr Cat. 2 to Repr. Cat. 3 is an observation that Met-Hb formation appears often, although not always, in animals at slightly lower exposure level than the degeneration or atrophy of spermatogenic epithelium. Thus, in line with this argument, lowering the exposure to protect against formation of Met-Hb will also protect against spermatotoxicity. This argument is valid and appropriate in the process of risk assessment and management which is different from hazard identification. The supporters of this view do not take into account that the aim of both DSD and CLP classification systems is to identify inherent hazardous properties of a substance and that hazard identification is separate from risk assessment or risk management. Consequent use of this argument would lead to a limitation of the classification of substances to the most sensitive endpoints and to distortion of a process of hazard identification, which is a starting point for risk assessment and management.

According to CLP regulation specific effects on the reproductive organs should be considered for classification for reproductive toxicity. Still it is noteworthy to note that nitrobenzene is the reproductive toxicant for animals in a range of doses that would allow to classify that substance to "STOT RE 1 (male gonads)" because the histopatological damage of spermatogenic epithelium was detected in animals exposed for 2 years by inhalation at dose level of 0.13mg/l, which is below guidance value for STOT RE category 1 equal to 0.2 mg/L/6hour/day (CLP regulation) and below 0.25 mg/L/6hour/day which is a guidance value for category Xn, R48/20(male gonads) for studies of 90 days duration (DSD regulation). This remark is made to indicate that the toxic effects in male gonads were seen at low exposure levels.

The methemoglobin formation and spermatotoxicity should be thus regarded as inherent toxic properties of nitrobenzene with different mode of action and classified in accordance with criteria given in DSD and CLP regulations.

Taking the above consideration into account, RAC is of the opinion that there is sufficient evidence to classify nitrobenzene according to the CLP regulation for the reproductive toxicity category 1B Presumed human reproductive toxicant with hazard statement H360F (Repr. 1B, H360F) and according to Directive 548/67 to Repr. Cat. 2; R60 – may impair fertility.

Effects on or via lactation

In a two-generation study in Sprague-Dawley rats (Dodd et al. 1987) the only significant finding in the litters derived from rats exposed at the highest concentration of 0.204mg/L (40 ppm) was an approximate 12% decrease in the mean body weight of F1 pups on Postnatal Day 21. There was no reduction of body weight of F_2 weanlings on postnatal day 21 in any exposed groups, which suggest that this body weight decrease in F_1 generation was not treatment related. No weight differences had been noted between all dose groups and control animals at parturition. The live birth index, the survival index on day 1 and on day 4 as well as lactation index of F1 and F2 generations were not affected by inhalation exposure to nitrobenzene at concentration of 0.005, 0.051 and 0.204 mg/L. The mean survival indices for all groups, all generations, ranged between 93 and 100%. The maternal toxicity of F0 lactating dams exposed at 0.0204 mg/L was not demonstrated in a 2-generation study of Dodd at al. (1987), but it was only based on lack of visible clinical signs of abnormalities. The levels of methemoglobin were not measured in a 2- generation study of Dodd at al. (1987), however taking into account the increases of methemoglobin to ca. 10%, observed in F344 rats exposed for 90 days by inhalation at comparable concentration of 0.26mg/l (CIIT 1984, Hamm 1984), it is highly probable that methemoglobin levels in lactating mothers exposed at 0.204mg/l were severely increased too. In rats exposed for 90 days to nitrobenzene by inhalation at concentration of 0.26 mg/l (Hamm,1984) comparable to concentration used in the study of Dodd et al. (1987), the increased level of methemoglobin was associated with increase in bilirubin, fibrosis of spleen and hyaline degeneration in kidney. Therefore it is concluded the slight reduction of weight of weanlings in first generation born and feed during lactation by mothers exposed to nitrobenzene at 0.204mg/l (Dodd et al. 1987) occurred as a secondary, indirect effect of marked maternal toxicity leading to haemolytic anaemia of lactating mothers.

In the one-generation study of Mitsumori et al. 1994 female rats were receiving by gavage nitrobenzene at doses of 20, 60 and 100 mg/kg for 14 days before mating, during mating, gestation and up to 3rd day after parturition at doses of 20, 60 and 100mg/kg. No pups born to female rats exposed at 100mg/kg survived till 4 day after parturition, viability of pups during first 4 days of life of females exposed at 60mg/kg was reduced to 66.9%, while viability of those exposed at 20 mg/kg (99%) was equal viability of control pups (99.1%). The results of reduced viability and reduced body weight gain of pups observed in this study only for 4 first days of life (Mitsumori at al. 1994) could be interpreted as showing effect on or via lactation, if the lactating mothers were not severely intoxicated. In fact, the doses of 60 and 100 mg/kg given by gavage in the study of Mitsumori et al. 1994 were causing severe intoxication of mothers. The animals exposed at 100mg/kg/day starting from 13 day of exposure exhibited piloerection, salivation, emaciation and anaemia. In some of these animals torticolitis, circling movement and abnormal gait were observed. Both males and females showed decrease in food consumption and decrease in body weight gain. Seven females out of 10 in the 100mg/kg group died during gestation and 2 during lactation period, which demonstrate severity of intoxication with nitrobenzene at this dose. In the 60mg/kg group the anaemia was seen in 6 of 10 rats from day 19 of pregnancy and neurological signs such as abnormal gait and torticolitis were observed in one rat from day 1 of lactation. The females in the 60mg/kg group also showed decreased food consumption and inhibition of body weight gain during lactation. One female each from the 60 and 20 mg/kg died during lactation (Mitsumori et al. 1994). The levels of haemoglobin and RBC in males rats exposed at doses of 20, 60 and 100mg/kg were significantly reduced (females were not examined) and level of methemoglobin was significantly increased in comparison with control rats. Having in mind that the reduction in viability of pups during 4 first days of lactation and reduced body weight gain of pups on day 4 of lactation was due to maternal toxicity these effects do not warrant classification for lactation effects.

Taking into account the data in the background document summarized above showing that alterations in viability and body weight gain of pups during lactation observed in studies on rats were due to severe maternal toxicity RAC is of the opinion, that

nitrobenzene should not be classified within CLP or DSD system for lactation effects. Thus the opinion proposed by the Dossier Submitter is not supported.

During public consultation some MSCAs were not in favour to classify nitrobenzene for lactational effects and some were in favour to do so.

Specific target organ toxicity

There are several studies on animals exposed by:

- oral route (NTP 1983a cited in US EPA 2009; Shimo et al. 1994; Burns et al;1994; Mitsumori et al. 1994),
- inhalation (Medinsky and Iron 1985; DuPont 1981; Hamm 1984, CIIT 1993) or
- dermal route (NTP 1983b cited in US EPA 2009)

which have been reviewed in the background document and can be used for assessing specific target organ toxicity.

These studies demonstrate that the most sensitive cells to toxicity of nitrobenzene are erythrocytes where nitrobenzene induces formation of methemoglobin, which leads to premature destruction of erythrocytes, reduction of haemoglobin level in blood, increased medullary and extramedullary haematopoiesis, increased percentage of reticulocytes in blood, deposition of hemosiderin in spleen, liver and kidney with eventual fibrosis of these organs.
According to Regulation No. 1272 (section 3.9.2.) substances are classified as specific target organ toxicants following repeated exposure by the use of expert judgement on the basis of the weight of all available evidence. Substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following repeated exposure are assigned to the STOT-RE categories. According to Directive 67/548/EEC only effects causing serious damage to health such as death, clear functional disturbance or morphological changes should be considered for classification. It should be noted that as defined Annex I of the Regulation (EC) No 1272/2008 (3.9.2.8.1.) there are some effects in humans and/or animals that do not justify classification. Such effects include, but are not limited to:

> (a) clinical observations or small changes in bodyweight gain, food consumption or water intake that have toxicological importance but that do not, by themselves, indicate 'significant' toxicity;
> (b) small changes in clinical biochemistry, haematology or urinalysis parameters and/or transient effects, when such changes or effects are of doubtful or minimal toxicological importance;
> (c) changes in organ weights with no evidence of organ dysfunction;
> (d) adaptive responses that are not considered toxicologically relevant;
> (e) substance-induced species-specific mechanisms of toxicity, i.e. demonstrated with reasonable certainty to be not relevant for human health, shall not justify classification.

<u>Oral route</u>

The NTP 1983a study was chosen as key study to demonstrate the specific target organ toxicity due to oral exposure of nitrobenzene. The results of other studies as reviewed and compared with classification criteria in background document are in support of the conclusion drawn on the results of this key study.

Effects in rats justifying classification
In the 90-day gavage study on rats (NTP, 1983a cited from US EPA, 2009) the severity of effects observed in F344 rats at the dose levels of 37.5 - 150mg/kg such as lethality (

only high dose), pigmentation (hemosiderosis) in kidney of female rats (75-150 mg/kg) combined with 10% or more reduction in level of functional haemoglobin, reduction in hematocrit, number of red blood cells, increase in percentage of reticulocytes linked with higher incidence of moderate spleen congestion (in females 37.5- 150 mg/kg, and in males 75-150mg/kg) and liver congestion (males 150 mg/kg), although without fibrotic lesions are judged as meeting criteria of significant hematotoxicity and organ toxicity defined in the Guidance on the Application of Regulation (EC) No 1272/2008, section 3.9.2.5.2.

Effects in rats not justifying classification
The intensity of the haematological effect in rats leading to less than 10% reduction in level of functional haemoglobin being a sum of % reduction of Hb and % increase in MetHb at the dose of 9.38 – 18.75 mg/kg not accompanied with significant microscopic changes in liver, kidney and brain and only with low increase in incidence of mild histopathological changes in spleen without fibrotic changes in liver, kidney or spleen do not meet criteria of significant hematotoxicity as defined in the CLP guidance or guidance developed for classification of substances inducing haemolytic anaemia within DSD framework (Muller et al. 2006).

Effects in mice not justifying classification
In the 90-day gavage study (NTP, 1983a cited from US EPA, 2009) the effects observed in B6C3F1 mice exposed by gavage to nitrobenzene for 90 days do not meet classification criteria of STOT RE 2 because hematotoxicity linked with microscopic changes in internal organs were demonstrated only at doses of 150-300 mg/kg above a guidance value of ≤ 100 mg/kg/day (CLP criteria) and above a guidance value of ≤ 50 mg/kg/day for Xn, R48 in DSD classification criteria.

Conclusion: The effects observed in this study in F344 rats meet the classification criteria of STOT RE 2 (blood) with a hazard statement H373 because they demonstrated significant hematotoxicity below the guidance value of ≤ 100 mg/kg/day (CLP criteria). They also meet the classification criteria of category Xn, R48/22 because there were induced below a guidance value of ≤ 50 mg/kg/day for this category in DSD. The effects observed in this study in mice do not meet classification criteria at the level of exposure above those defined by the DSD and CLP guidance values.

However, as it was already considered in this opinion, humans are much more sensitive then rats to formation of Met-Hb, which should be taken into account in the weight of evidence approach underpinning decision on classification. Formation of Met-Hb, in response to repeated exposure to nitrobenzene, may cause secondary toxic effects in internal organs such as spleen, liver, kidney, brain and lungs, thus the high difference between humans and rats in susceptibility to induction of Met-Hb should be taken into consideration in hazard classification.

The criteria for Xn, R48/22 (DSD) and STOT RE 2 (blood) - H373 are met if the animal studies are assessed isolated. The effects observed in target organs are assessed to be relevant to humans, however because of the higher sensitivity of humans to Met-Hb forming action of nitrobenzene humans are more sensitive than animals to toxicity of this substance. Taking the higher sensitivity in humans into consideration, RAC recommends that nitrobenzene is classified as STOT RE 1 - H372 Causes damage to organs (blood), and T: R48/25 (DSD).

This classification is in agreement with the existing classification, a proposal of Dossier Submitter, opinion of TC C&L and opinions of some MSCAs expressed during public consultation.

Inhalation exposure

The 90-day inhalation study on rats and mice (Hamm 1984) was chosen as key studies to demonstrate the specific target organ toxicity due to inhalation of nitrobenzene. The results of other studies as reviewed and compared with classification criteria in background document are in support of the conclusion drawn on the results of this key study.

Effects in rats justifying classification
In a 90-day inhalation study on rats and mice (CIIT study,1984; Hamm,1984) a repeated exposure (90 days) to nitrobenzene at conc. of 0.26 mg/l induced marked increase in the concentration of methemoglobin up to 10% in F344 and CD rats. In addition at this concentration nitrobenzene caused in all F344 rats of either sex an increase in spleen weight, congestion of spleen, proliferative fibrotic capsular lesions and increases in extramedullary haematopoiesis in spleen. In CD rats the sinusoidal congestion, increased extramedullary haematopoiesis, and numbers of hemosiderin-laden macrophages infiltrating the red pulp in spleen, and an increase in the thickness (fibrosis) of the splenic capsule were noted. In both strains of rats (F344 and CD), exposure to nitrobenzene at the concentration of 0.26 mg/l induced toxic nephrosis. These effects meet the criteria of significant hematotoxicity in the Guidance on the Application of Regulation (EC) No 1272/2008 such as e.g. significant increase in hemosiderosis in the spleen, liver or kidney in combination with microscopic effects like necrosis, fibrosis or cirrhosis with reduction in Hb level and increase in MetHb level.

Effects in rats not justifying classification
At the concentration of 0.026 and 0.082 mg /l, i.e. lower than the limit value of 0.2 mg/l/6h/day for STOT Category 1 nitrobenzene induced low increases in concentration of methemoglobin in blood from 1.2% in control F344 males rats and 1.6% in control female F344 rats to 3.0 -4.4 % in male F344 rats and 3.2-3.9% in female F344 rats. However, these small increase in levels of methemoglobin were not associated in study report with significant heamosiderosis in combination with microscopic changes such as necrosis, fibrosis or cirrhosis or with other effects meeting classification criteria for substances causing haemolytic anaemia (CIIT study,1984; Hamm,1984). Therefore classification for category STOT RE 1 in the basis of this study is not warranted.

In the chronic inhalation study (Cattley et al. 1994; CIIT, 1993) the hematotoxic effects in rats exposed for 2 years at 0.13mg/l and mice exposed at 0.26mg/l were limited to mild increase in level of methemoglobin not exceeding 6% (with 1.39 – 2.75% in control animal), reduction in functional Hb level in blood of approximately 12 % in comparison with controls, reduction in RBC counts not exceeding 10% in comparison with control values, thus in the light of legal requirements and guideline on the application of the CLP regulation or DSD regulation such toxic changes were alone not sufficient to classify them as significant hematotoxicity. The observed haematological changes were not accompanied in by the histopatological changes in spleen, liver and kidney typical for long-lasting haemolytic anaemia. Although pigmentation in spleen was slightly more frequent (hemosiderosis) in highest exposed group than in controls, it was not leading to fibrosis of spleen, which was observed in the 90-day inhalation study at higher nitrobenzene concentration of 0.26mg/l. Thus results of this chronic experiment do not warrant classification of nitrobenzene to STOT RE 1 due to its hematotoxic effect.

Conclusions:
Taking into account that the significant and severe hematotoxic effects in animals were observed in blood and internal organs at 0.26mg/l, thus in a range of 0.2 and ≤ 1.0 mg/l/6h/day nitrobenzene meets criteria for STOT RE 2 (blood) with a hazard statement H 373. Since the concentration of 0.26mg/l inducing significant organ toxicity is very

close to DSD guidance value of ≤ 0.25 mg/l/6h/day for category Xn, R48/20 it is considered appropriate to classify nitrobenzene to this category based on data derived from studies on rodents.

However, as it was already considered in this opinion, humans are much more sensitive then rats to formation of Met-Hb, which should be taken into account in the weight of evidence approach underpinning decision on classification. Formation of Met-Hb, in response to repeated exposure to nitrobenzene, may cause secondary toxic effects in internal organs such as spleen, liver, kidney, brain and lungs, thus the high difference between humans and rats in susceptibility to induction of Met-Hb should be taken into consideration in hazard classification.

Therefore, in the opinion of RAC the classification derived solely on animal data - Xn, R48/20 (DSD) and STOT RE 2 (blood) with a hazard statement H373 – is not relevant for humans, because they are more sensitive than rats or mice to Met-Hb formation, thus the repeated specific target organ toxicity of nitrobenzene by inhalation should by classified T: R48/23 (DSD) and STOT RE 1 - H372 Causes damage to organs (blood).

This classification is in agreement with the existing classification, a proposal of Dossier Submitter, opinion of TC C&L and opinions of some MSCAs expressed during public consultation.

Dermal route

NTP sponsored a 90-day skin painting toxicological study (NTP, 1983b cited from US EPA, 2009) with nitrobenzene in F344 rats and B6C3F1 mice. The authors treated F344 rats and B6C3F1 mice (10 animals/sex/group) with 50, 100, 200, 400, and 800 mg/kg-day nitrobenzene in acetone, the responses being compared with those in animals painted with acetone alone.

Effects in rats and mice justifying classification

The following significantly toxic effects, meeting classification criteria in CLP and DSD systems, were seen in F344 rats and B6C3F1 mice exposed dermally at 50, 100 and 200 mg/kg bw/day for 13 weeks:

- in male rats - spleen congestion starting from 50 mg/kg, lung congestion and lymphoid atrophy starting at 100 mg/kg;
- in female rats - spleen haematopoiesis and congestion, lung congestion at 100mg/kg, haemorrhage in brain starting with a dose 100mg/kg
- in male mice: lung congestion and spleen haematopoiesis starting at 50 mg/kg,
- in female mice - fatty change in the adrenal cortex in addition to the haematological findings noted at the lowest dose of 50 mg/kg bw/d.

Conclusions: These effects meet criteria of severe adverse health effects at the dose levels in a range between 20 and 200 mg/bw /day for STOT RE, Category 2 (CLP) with a hazard statement H 373 or in dose levels >10 mg/kg to ≤100 mg/kg (bodyweight)/day for category Xn, R48/21 (DSD).

However, as it was already considered in this opinion, humans are much more sensitive then rats to formation of Met-Hb, which should be taken into account in the weight of evidence approach underpinning decision on classification. Formation of Met-Hb, in response to repeated exposure to nitrobenzene, may cause secondary toxic effects in internal organs such as spleen, liver, kidney, brain and lungs, thus the high difference

between humans and rats in susceptibility to induction of Met-Hb should be taken into consideration in hazard classification.

Therefore, in the opinion of RAC the classification derived solely on animal data - Xn, R48/21 (DSD) and STOT RE 2 (blood) with a hazard statement H373 – is not relevant for humans because of the higher sensitivity of humans to Met-Hb forming action of nitrobenzene, thus the repeated specific target organ toxicity of nitrobenzene by inhalation should by classified T: R48/24 (DSD) and STOT RE 1 - H372 Causes damage to organs (blood)

This classification is in agreement with the existing classification, a proposal of Dossier Submitter, opinion of TC C&L and opinions of some MSCAs expressed during public consultation.

Conclusion: Having in mind the above arguments RAC is of the opinion that specific target organ toxicity of nitrobenzene should be classified according to CLP regulation in category STOT RE 1 (blood) - H372 Causes damage to organs (blood) and according to DSD regulation for category T, R48/23/24/25.

This classification is in agreement with the existing classification, a proposal of Dossier Submitter, opinion of TC C&L and opinions of some MSCAs expressed during public consultation.

Aspiration toxicity

The dossier submitter originally proposed classification for aspiration toxicity (Asp. Tox 1 – H304 (CLP), Xn; R65 (DSD), based on an estimated kinematic viscosity of less than 20.5 mm^2/s at 40°C. However, during public consultation, a comment was received from an industrial association arguing that the classification criteria in Annex I of CLP (section 3.10.2) should only be applied for pure hydrocarbons and for substances with surface tension below 33mN/m at 25 degrees. The dossier submitter argues that pure hydrocarbons should be considered an example of classes likely to exhibit aspiration hazardous properties. Nevertheless, upon further reflection on uncertainty of kinematic viscosity of nitrobenzene and based on a high surface tension (42 mN/m) and existing classification for Acute Toxicity, the dossier submitter no longer considers the classification of Nitrobenzene for Aspiration Toxicity warranted. The withdrawal of the proposal was reflected in the revised CLH report submitted after public consultation. RAC taking into account lack of sufficient data for classification agrees with the dossier submitter that classification for Aspiration Toxicity is not warranted and this is reflected in the opinion tables above.

Environmental Hazards

The existing classification of N R51/53 has been added to Annex I of Directive 67/548/EEC by the 22nd ATP in 1996. The summary record of the TC CnL meeting held on 13-14 December 1994, provides very limited information about the acute toxicity data basis for this classification. As it is described in the summary report of Working Group on the Classification and Labeling of Dangerous Substances: Environmental Effects; Meeting at ECB Ispra, 13-14 December 1994 (European Commission, Directorate General XII – JRC; ECBI/24/94 - Rev. 1) for Nitrobenzene (C160, 609-003-00-7): "DE reported that the initial proposal was R52/53. However, based on acute toxicity data,

Industry proposed R51 instead and stated that the compound was biodegradable and recommended no classification. However, it was proposed that the compound be classified as R51/53. Conclusion: It was agreed that the compound be classified as N; R51/53."

However almost 14 years later, in the Risk Assessment Report prepared under the Existing Substances Regulation (RAR 2007,), all available ecotoxicological test data had been scrutinised and validated. Very few acute test results would meet the criterion for R51 classification, but all of these are neither sufficiently documented nor reliable (cf. pp. 33-39 of RAR 2007). In contrast, all valid information presented in this background document provides consistent justification for the proposed classification R52/53 (H412).

The acute aquatic toxicity indices provided in background document such as LC_{50} for fish or EC_{50} for invertebrates and ErC_{50} for alga are higher than 1 mg/l, thus according to CLP regulation and Directive 67/548/EWG nitrobenzene does not meet the criteria for acute environmental classification.

Nitrobenzene is not rapidly degradable (in 28-day ready-biodegradation studies nitrobenzene did not achieve the pass level. See section 4.1.2 of BD).
There are no adequate chronic toxicity data for nitrobenzene for all three tropic levels, therefore during classification nitrobenzene for chronic toxicity, according to CLP, both criteria given in Table 4.1.0(b) (i) or 4.1.0(b) (ii) and in Table 4.1.0(b) (iii) should be assessed.
The classification of nitrobenzene, according to CLP, was based on Table 4.1.0(b) (iii) – the most stringent outcome. The following information were used for classification:
- aquatic acute toxicity indices for fish, invertebrates and alga obtained during tests were between 10 mg/l and 100 mg/l
- the substance is not rapidly degradable.

The same information should be used during classification nitrobenzene according to Directive 67/548/EWG.

Conclusions on environmental classification
There is sufficient evidence to classify nitrobenzene according CLP and Directive 67/548/EEC for environmental classification. According to CLP nitrobenzene should be classified as Aquatic Chronic Cat. 3; H412 (Harmful to aquatic life with long lasting effects) and according to Directive 67/548/EEC as dangerous to the environment with risk phrase R52/53 (Harmful to aquatic organisms, may cause long-term effects in the aquatic environment).

The same classification of environmental hazards was proposed by the dossier submitter and supported in public consultation by several MSCA.

Conclusion on proposal to split entry based on presence of classified impurity

The Dossier submitter has proposed to split the entry for Nitrobenzene based on the concentration of Benzene, a classified impurity (Annex VI index number 601-020-00-8). According to the manufacturers' information, Benzene can be present as an impurity up to 0.3%. The dossier submitter proposes to introduce two entries on Annex VI for Nitrobenzene, one with impurities of less than 0.1% (except water) and another for Nitrobenzene with benzene as an impurity at or above 0.1% but below 0.3%. Several Member States supported this idea during public consultation.

The difference between the two entries is based solely on the generic concentration limits applicable to the Benzene classification. Article 11(1) of the CLP regulation lays out that

"*Where a substance contains another substance, itself classified as hazardous, whether in the form of an identified impurity, additive or individual constituent, this shall be taken into account for the purposes of classification, if the concentration of the identified impurity, additive or individual constituent is equal to, or greater than, the applicable cut-off value…".* The existing entry for Nitrobenzene does not take into account the presence of any impurities.

Taken the above into account, RAC believes that the entry for Nitrobenzene should not specify the presence or absence of any impurities but rather specify the substance in its pure form. Should a substance placed on the market differ from the one specified in Annex VI, any impurities should be taken into account and the substance classified accordingly.

Additional information

The Background Document, attached as Annex 1, gives the detailed scientific grounds for the Opinion.

ANNEXES:

Annex 1 Background Document (BD)[1]

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

[1] The Background Document (BD) supporting the opinion contains scientific justifications for the CLH proposal. The BD is based on the CLH report prepared by a dossier submitter. The original CLH report may need to be changed as a result of the comments and contributions received during the public consultation(s) and the comments by and discussions in the Committees.