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Note on reference dose-response relationship for the carcinogenicity of pitch, coal tar, high temperature and on PBT and vPvB properties

Preface

At the 22nd meeting of the Committee for Risk Assessment (RAC) in September 2012, the ECHA Secretariat presented a proposal to set DNELs and dose-response relationships for substances prior to receiving applications for authorisation. This was initially approved by RAC as a trial exercise. However, in early 2015, ECHA agreed to continue supporting the practise for Annex XIV substances, recognising its value to the Authorisation process and its efficiency[1].

The DNELs and dose-response relationships so derived serve as non-legally binding 'reference values'. They provide applicants with a clear signal as to how RAC is likely to evaluate these important elements of the risk assessment of an application for authorisation.

Reference values in the form of DNELs for threshold substances and/or dose-response relationships for non-threshold (mainly) carcinogens are published in advance of applications for authorisation, so providing greater consistency and better use of the legally defined periods of opinion-development in the Committee for Risk Assessment (RAC).

[1] At the Conference on "Lessons learnt on Applications for Authorisation" co-organised by ECHA and the European Commission that took place on 10-11 February 2015.

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1 Summary

CTPHT is included in Annex XIV of REACH for its intrinsic properties Carcinogenic (category 1B); persistent, bioaccumulative and toxic (PBT); and very persistent and very bioaccumulative (vPvB).

Since CTPHT is a PBT and vPvB substance, the applicant is advised to focus on reducing the exposures and emissions to humans and the environment to as low a level as is technically and practically possible.

CTPHT is considered to be a non-threshold carcinogen. Lung, bladder and skin cancers are identified as the key cancer risk endpoints for exposure to CTPHT, these are the cancers for which data specific to CTPHT exposures exist from animal studies and industrial epidemiology. In the absence of information to assess possible overlaps of people developing lung cancer, bladder cancer and skin cancer, applicants are advised to assume these cancer risks are independent. Applicants should ensure that other cancer types are also considered at least in a qualitative manner in the risk assessment and the socio-economic analysis.

An overview of reference dose-response relationships for the carcinogenic properties of CTPHT is presented in Table 1.

Table 1 Overview of reference dose-response relationships for the carcinogenic properties of CTPHT

Route	Cancer type	Lifetime excess risk	
		Workers	General population
Inhalation	lung cancer	5.6×10^{-6} per ng/m^3 [(a)]	3.0×10^{-5} per ng/m^3
	bladder cancer	4×10^{-6} per ng/m^3 [(a)]	2.1×10^{-5} per ng/m^3
Dermal	skin cancer	1.3×10^{-3} per ng BaP/cm^2/day	Not derived [(c)]
Oral	cancer	Not relevant	2.06×10^{-3} per µg PAH4/kg bw/day 1.43×10^{-3} per µg PAH8/kg bw/day

[a] Exposure levels in air can also be derived from urinary 1-OHP or 3-OHBaP biomonitoring data using the relationships:

- urinary post-shift concentration of 3-OHBaP (µmol/mol creatinine) = 0.001835 × 8h TWA BaP concentration in air (µg/m^3) + 0.1729
- urinary post-shift concentration of 1-OHP (µmol/mol creatinine) = 11.1 × 8h TWA BaP concentration in air (µg/m^3) + 1.13

[c] No significant exposure of the general population by the dermal route is envisaged. Therefore, no dose-response was derived. However, applicants may use the relationship derived for dermal cancer for workers and convert it to general population as relevant.

2 Relevance of endpoints

Pitch, coal tar, high temperature (CTPHT) (EC 266-028-2, CAS 65996-93-2) is the residue from the distillation of high temperature coal tar. It is a black solid with an approximate softening point from 30 °C to 180 °C. CTPHT is composed primarily of a complex mixture of three or more membered condensed ring aromatic hydrocarbons.

In June 2017, CTPHT was included in Annex XIV of REACH for its intrinsic properties Carcinogenic (category 1B); persistent, bioaccumulative and toxic (PBT); and very persistent and very

bioaccumulative (vPvB).[2] **It has a latest application date of 4 April 2019 and a sunset date of 4 October 2020**[3].

For substances for which it is not possible to determine a threshold, applicants can apply for authorisation based on Article 60(4), i.e. the socio-economic analysis route. The Chemical Safety Report (CSR)[4] is focused on the risks related to the intrinsic properties specified in Annex XIV and the socio-economic analysis (SEA) should in turn consider the impacts related to such risks. However, for an authorisation to be granted, the applicant should also demonstrate that there are no suitable alternatives. In this latter analysis it may be the case that other endpoints than those for which the substance was listed in 'Annex XIV' may also become relevant. Further advice on how the Committee for Socio-economic Analysis (SEAC) deals with the impacts and socio-economic aspects of PBT and vPvB substance is also available[5].

Reference dose-response relationships are presented in the current document for the carcinogenic properties (Carc. 1B; H350) listed in Annex XIV and advice on dealing with the Annex XIV-listed PBT and vPvB properties of CTPHT is also given in section 4.

Since ECHA's 6th Annex XIV recommendation, the harmonised classification of CTPHT has been amended[6]. The current harmonised classification is:

- Carc. 1A; H350
- Muta. 1B; H340
- Repr. 1B; H360FD

Although it is recognised that, with the exception of carcinogenicity, these propoperties are not part of the listing of CTPHT on Annex XIV or REACH, applicants for authorisation are advised to pay special attention to the endpoints toxicity to reproduction and germ cell mutagenicity (in addition to the endpoints listed in Annex XIV) when performing the analysis of alternatives[7].

3 Carcinogenicity

Pitch, coal tar, high temperature (CTPHT) is classified as carcinogen category 1A and germ cell mutagen category 1B. CTPHT is a "UVCB" substance with many constituents at variable concentrations, while some constituents are unknown. Over 400 compounds have been identified in coal tars, and probably as many as 10 000 are actually present (Trosset *et al.*, 1978; McNeil, 1983). In general, however, approximately 80% of the total carbon present in coal tars exists in aromatic form (ECHA, 2011). The group of constituents that are considered responsible for the systemic and local carcinogenic effects of CTPHT are polycyclic aromatic hydrocarbons (PAHs) (ECHA, 2015).

[2] COMMISSION REGULATION (EU) 2017/999 of 13 June 2017
[3] https://echa.europa.eu/authorisation-list/-/dislist/details/0b0236e1804df1dc
[4] An update of the CSR submitted for registration purposes may be advisable.
[5] https://echa.europa.eu/documents/10162/13580/evaluation_pbt_vpvb_substances_seac_en.pdf
[6] The 5th Adaptation to Technical Progress (Commission Regulation (EU) 944/2013) amended the classification of CTPHT in Annex VI, part 3, Table 3.1 (the list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008 (Classification, Labelling and Packaging; CLP). This new classification is applicable from 1 April 2016. However, the harmonised classification as Aquatic Acute 1 (H400) and Aquatic Chronic 1 (H410) was later annulled by a judgement of the Court (http://curia.europa.eu/juris/document/document_print.jsf?doclang=EN&text=&pageIndex=0&part=1&mode=lst&docid=197001&occ=first&dir=&cid=43679).
[7] Endpoints relevant to the authorisation are also discussed in section 5 of the document: "How RAC and SEAC intend to evaluate the applications" (common approach of RAC and SEAC in opinion development on applications for authorisation, agreed RAC-20 / SEAC-14, 24/03/2012). Link: https://echa.europa.eu/documents/10162/13555/common_approach_rac_seac_en.pdf

3.1 Mechanism of carcinogenic action

Many PAHs share the same genotoxic mechanism of action, i.e., metabolic activation to electrophilic dihydrodiol epoxides and/or quinones which are capable of covalent binding to DNA (WHO, 1998). The DNA adducts thus formed may cause mutations.

The variation in carcinogenic potencies of PAHs is most probably associated with the structural differences between adducts and the subsequent effects on removal by DNA repair mechanisms. However, it could also be a result of changes in DNA polymerase activity and incorrect base-pair insertion resulting from post-lesion DNA synthesis. Mutations can activate oncogenes or inactivate tumour suppressor genes, i.e. p53 gene. Many PAHs are ligands for the aryl hydrocarbon receptor (AhR), which has different roles involved in metabolism including induction of bioactivating enzymes. Epigenetic changes including DNA methylation and telomere dysfunction have been also reported after exposure to complex PAH mixtures in human workers and following *in vivo* mouse exposure.

Experiments on interactions of PAH in both binary and complex mixtures on DNA adduct levels reported both less-than-additive and more-than-additive effects. In a dose-response study performed in mice (Jarvis *et al.*, 2014), it was found that mixtures of 5 PAHs exhibited more-than-additive effects at low doses and less-than-additive effects at high doses compared to individual PAH exposure. This paradoxical finding (i.e. non-linear dose-effect relationship) probably resulted from competitive inhibition of the metabolising enzymes at higher doses and hence decreased amounts of DNA-reactive metabolites, and is in accordance with the findings of studies on binary and complex PAH mixtures (Jarvis *et al.*, 2014).

The carcinogenicity of benzo[*a*]pyrene (BaP), the most extensively studied PAH, is well documented in animal models (IARC, 2010; Xu *et al.*, 2009; Jiang *et al.*, 2007; Jiang *et al.*, 2005; Xue and Warshawsky, 2005; Ramesh *et al.*, 2004; Boström *et al.*, 2002; Penning *et al.*, 1999; Harvey, 1996; ATSDR, 1995; Cavalieri and Rogan, 1995). **The primary mode of action by which BaP induces carcinogenicity is genotoxicity.** This mode of action is presumed to apply to all tumour types and is relevant for all routes of exposure. The general sequence of key events (KEs) associated with genotoxic mode of action for BaP is as follows:

1. Bioactivation of BaP to DNA-reactive metabolites via three possible metabolic activation pathways: a diol epoxide pathway, a radical cation pathway, and an o-quinone pathway;
2. Direct DNA damage by reactive metabolites, including the formation of DNA adducts and ROS-mediated damage;
3. Formation and fixation of DNA mutations, particularly in tumour suppressor genes or oncogenes associated with tumour initiation; and
4. Clonal expansion of mutated cells during the promotion and progression phases of cancer development.

BaP can act as both an initiator and a promoter of carcinogenesis. Initiation by direct DNA damage (key event 2) can occur via all three metabolic pathways of BaP. DNA damage that is not adequately repaired may lead to mutations (key event 3). These mutations can undergo clonal expansion (key event 4) enabled by multiple mechanisms which are also induced by BaP. These latter include AhR binding leading to an upregulation of genes related to biotransformation, growth, and differentiation, and regenerative cell proliferation resulting from cytotoxicity and a sustained inflammatory response. However, there is insufficient evidence that these mechanisms, which contribute to the promotion and progression phases of cancer development, act independently of DNA damage and mutation to produce BaP-induced tumours. The available human, animal, and in vitro evidence all supports mutagenicity as the primary

mode of action by which BaP induces carcinogenesis (US EPA, 2017).

Bitumen and coal tar fume condensates obtained at various temperatures were all found to be mutagenic in the Ames test (Binet *et al.* 2002). Metabolic activation was needed to obtain positive results.

In addition to genotoxicity, there are suspected interactions of BaP with various constituents of the proteome. Such non-genotoxic pathways are a matter of recent research (Verma *et al.* 2012). For example, BaP and its metabolites are implicated in oxidative stress-mediated pathways (formation of orthoquinone/ reactive oxygen species, and AhR mechanism), immunosuppression through AhR-mediated CYP-derived metabolites (diolepoxides, quinones), as well as epigenic mechanisms involving cell proliferation, PAH-induced apoptosis and DNA methylation (IARC, 2012).

Conclusion

In conclusion, the evidence indicates a primarily genotoxic non-threshold mechanism of action for the local and systemic carcinogenicity of CTPHT.

3.2 Potency of PAH constituents

Numerous PAHs have been investigated for their carcinogenic potency. The structural characteristics of PAHs understandably influence both their metabolic activation and the stereochemistry of DNA binding.

Comparisons of the potencies of PAH molecules show that the genotoxic potency increases with the number of rings; the carcinogenic 3- or 4-ring PAHs are clearly less potent than their 5- and 6-ring counterparts (see IARC 1983, 2010). Compounds with a bay region - an indentation caused by an angular benzene ring attached- are strong carcinogens. Compounds with a fjord region - a distortion caused when a bay region is methylated or closed by an additional benzo ring - are even more potent carcinogens (SCOEL, 2016).

DECOS (2006) stated that dibenz[*a,h*]anthracene (a 5-ring PAH) appears to be equipotent or somewhat more potent than BaP, whereas other 5-ring PAHs tested (e.g., benzofluoranthenes, benzo[*e*]pyrene) are less or much less potent. As a result, in estimating cancer risk of complex PAH mixtures in which BaP is used as an exposure indicator for the whole PAH mixture, estimated risk values may be over- or underestimated (DECOS, 2006). However, at the present time BaP may serve as an acceptable genotoxic exposure indicator for PAH mixtures (DECOS, 2006), assuming that any change in concentration of measured BaP is associated with corresponding proportional change in concentration of other PAHs as well.

3.3 Bioavailability

No data are available regarding the absorption of CTPHT from inhalation, dermal and oral exposure, but information is available for PAH constituents.

Toxicologically relevant PAHs among the components of CTPHT can be absorbed orally, by inhalation and through the skin. Absorption profiles are different for the identified toxicologically relevant components of CTPHT, as illustrated by different absorption rates for different non-particle-bound PAHs (ECHA, 2011). Due to the variable physical form and composition of CTPHT and coal tar pitch volatiles, the predictive value of absorption studies conducted with non-

particle-bound PAHs is limited (ECHA, 2011). Absorption after inhalation of particle-bound PAHs depends on particle size. The smaller the particles, the more extensive the PAHs elute from the particles (ECHA, 2011).

Inhalation route

When heated to high temperatures during its production and industrial uses, CTPHT can release mixtures of PAHs, commonly referred to as coal tar pitch volatiles (CTPVs). No data are available on exact quantitative estimates of PAH absorption in human lungs.

Animal studies show that BaP is absorbed by inhalation. PAHs are generally lipophilic compounds that can cross the lungs through passive diffusion and partitioning into lipids and aqueous compartments of cells.

Inhalation of BaP by laboratory animals can lead to rapid absorption from the lungs into the systemic circulation. Maximal BaP concentrations in plasma were achieved 1 hour after nose-only inhalational exposure of rats to BaP–carbon black aerosol (0, 0.1, 1.0 and 2.5 mg/m^3 for 4 hours); only trace amounts were detectable 5 hours later (Ramesh *et al.*, 2001a). In rats, BaP is rapidly absorbed in the lungs following intratracheal instillation of radiolabelled BaP dissolved in triethylene glycol (Weyand *et al.*, 1986).

The absorption of PAHs may be influenced by carrier particles. PAHs may be dissolved from deposited particles, with the remainder generally eliminated by bronchial mucociliary clearance. However, the PAH in particles may remain in the lungs for a longer time (WHO, 2010). The kinetics of lipophilic PAHs in lungs suggest that, after deposition in lungs, there is a rapid systemic exposure to BaP after inhalation of PAH-containing particles. Intracellular BaP concentrations are higher in the tracheobronchial region than the alveolar region and in the epithelium lining the airways, and particles may act as a sink leading to long-term exposure to BaP in lungs and local lymph nodes (WHO, 2010). Gerde *et al.* (2001) showed that the fraction of BaP in diesel particles was quickly desorbed and absorbed into circulation through type I epithelial cells in the alveolar region and systemically rapidly metabolized. The fraction deposited in the tracheobronchial region was more slowly absorbed into circulation. A sizeable fraction (up to 30%) of BaP remained on the surface of particles in lungs and in lymph nodes for several months (Gerde *et al.*, 2001).

Oral route

The oral route is relevant for exposure of humans via the environment. Absorption of BaP following ingestion is low in humans, while oral absorption in animals varies among the PAH compounds depending on the lipophilicity, more lipophilic PAHs being better absorbed. Lipophilic vehicles such as oils facilitate the absorption from gastrointestinal tract. The oral bioavailability of BaP in rats has been estimated to be 10% (Foth *et al.*, 1988) or 40% (Ramesh *et al.*, 2001b), depending on the BaP dose administered (3 µg/kg bw or 100 mg/kg bw, respectively).

Dermal route

Percutaneous absorption of PAHs from solutions appears to be rapid for both humans and animals, but the extent of absorption is variable and may be affected by the vehicle used for administration (ATSDR, 1995). Skin absorption of PAHs adsorbed on the surface of particles is slower compared to solutions (ATSDR, 1995).

When a coal tar ointment was applied to several anatomical sites of human volunteers (workers from a coke plant), absorption rate constants ranged from 0.036 to 0.135/hour, suggesting that 20−56% of the dose would be absorbed within 6 hours (van Rooij *et al.*, 1993c). Dermal absorption rates varied 69% between different anatomical sites (forehead, shoulder, forearm,

palmar side of the hand, groin, and ankle) and only 7% between different individual volunteers. Based on 1-hydroxypyrene (1-OHP) excretion as a PAH marker it was estimated that after coal-tar ointment application on skin, 0.3-1.4% of the pyrene dose (about 2 µg pyrene/cm^2) became systemically available.

The overall absorbed amount of BaP in explanted viable skin samples from tissue donors exposed for 24 hours ranged from 0.09 to 2.6% of the dose (Wester *et al.*, 1990; Kao *et al.*, 1985). Skin from mice - which is much thinner - allowed for penetration of more than 10% of the applied dose (Kao *et al.*, 1985).

A study on blood perfused pig ears by van Rooij *et al.* (1995) tested absorption of PAHs into the perfusion blood. The study applied an average dose of 11 mg/cm^2 coal tar to 5 pig ears and subsequently analysed pyrene and 9 other PAHs in the perfusion blood to determine flux and cumulative absorption through pig skin over 200 minutes. The percentage of absorbed dose less than 0.2% was very low due to the overdose. The cumulative absorption ranged from 830 pmol/cm^2 for phenanthrene to less than 4 pmol/cm^2 for PAHs with more than 4 rings, such as BaP. The results showed that when pyrene is used as a marker compound for PAH absorption, the cumulative absorption of PAHs with a lower molecular weight will be underestimated (10-fold for fluorene, 12-fold for phenanthrene, about 2-fold for anthracene and fluoranthene). On the other hand, the percutaneous absorption of PAHs with a higher molecular weight than pyrene will be overestimated (ca. 7-fold for BaP, 100-fold for indeno[123-*cd*]pyrene). It is likely that this conclusion is also valid for dermal PAH absorption in man.

Bioavailability of BaP from coal tar pitch for local dermal effects is determined by two variables, dermal absorption and release/availability of BaP from the pitch matrix or semi-solid tar oils. Dermal absorption in rodents and humans is quite different. For a tar oil, an absorption 8-fold lower in human skin than in rat skin was determined (Fasano 2007a, b). It is assumed this also applies to mouse skin.

Conclusion

Based on the calculated dermal absorption of ten different PAHs from dermally applied coal tar to pig-ears (ranging from 1% to > 30%; van Rooij *et al.*, 1995) a worst case estimate of dermal absorption of PAHs from CTPHT of 30% may be proposed for experimental animals and humans. Since quantitative data on the absorption of PAHs from CTPHT and coal tar pitch volatiles after inhalation and oral exposure for humans are lacking, the default absorption from inhalation and oral exposure can be assumed to be 100% for both experimental animals and humans (ECHA, 2012).

3.4 Exposure indicators for cancer risk assessment

In addition to the variability and multitude of its PAH constituents, CTPHT (a solid at ambient temperatures) can undergo profound chemical transformations when heated to high temperature, causing the release of complex and variable mixtures, i.e. coal tar pitch volatiles. These mixtures have different composition than the CTPHT from which they are released, due to differential release rates of individual constituents and potential chemical reactions of the constituents at different temperatures. Aside from the variability of CTPHT itself and its volatiles, there are in general too many different PAH mixtures placed on the market to perform epidemiological or experimental studies on each and every individual whole mixture. Therefore, monitoring of exposure and risk assessment of complex PAH-mixtures is done by choosing key indicators which are responsible for a substantial part of the toxic effect.

3.4.1 Workers

Inhalation route

For occupational and environmental air measurements, BaP is usually chosen as the key indicator for PAH mixtures (e.g., Petry *et al.* 1996; Pufulete *et al.* 2004; Okona-Mensah *et al.*, 2005) because of (i) the large amount of available data on exposure and toxic effects of BaP, (ii) the availability of air-monitoring techniques for BaP, and (iii) the known and frequent human exposure to BaP in airborne PAHs.

According to Petry *et al.* (1996), who tested and analysed various samples from coke plants, graphite production plants, carbon anode production plants, silicon carbide production plants, bitumen paving work and worksites of metal recycling process, the contribution of the carcinogenic potency of BaP alone is in the range of 27 – 67% of the activity of the different PAH mixtures. Petry *et al.* (1996) concluded that using BaP as an indicator of exposure (surrogate), and not considering the PAH profile variability, was justified as a practical tool for the assessment of health risks from both occupational and environmental exposure to PAHs in air.

Another well-established approach is the relative potency approach, i.e. to estimate the cancer risk related to exposure of a PAH mixture based on measured exposure to several constituents of the mixture and based on the carcinogenic potency of these constituents relative to the carcinogenic potency of BaP (Petry *et al.*, 1996; Pufulete *et al.*, 2004; Sidorov *et al.*, 2013; Purcaro *et al.*, 2013; Jarvis *et al.*, 2014; Lemieux *et al.*, 2015). This component-based approach requires analytical determination of the carcinogenic constituents in the mixture. The quantitative estimate of the carcinogenic potency of selected individual components of the mixture is then expressed as the toxic equivalency value (TEQ) in relation to the potency of BaP (expressed as BaP equivalents). Petry *et al.* (1996) reported that the approach using BaP alone underestimated risks by a factor of 1.1 to 2 in comparison with a relative potency approach for several occupational environments and one city environment.

Overall, it seems appropriate to assess occupational risks by using airborne BaP as an indicator of exposure to coal tar derived products including PAH mixtures released when CTPHT is heated to high temperatures (coal tar pitch volatiles). This pragmatic approach allows epidemiologic data to be used, where exposure is expressed using BaP as an exposure indicator as well (see section 3.5).

Dermal route

Exposure via the dermal route contributes to systemic exposure and thus may contribute to the dose-response relationship derived from epidemiological studies for air concentrations. However, the predominant route of exposure will depend on the occupational setting, and, although cancers occur from systemic exposure, the route of exposure influences significantly the site where local cancers occur (i.e., lung cancers can be expected to arise mainly from exposure via inhalation and skin cancers from dermal exposure[8]).

In certain cases, dermal absorption of PAHs is of special concern and may be a significant or even the main route of exposure (ATSDR, 1995). A group of coke workers underwent an intensive skin monitoring program combined with personal air sampling and biological monitoring based on 1-OHP as a biomarker of exposure (van Rooij *et al.,* 1993c). Mean total skin contamination of 12 workers ranged between 21 and 166 µg pyrene per day. The dermal uptake of pyrene ranged between 4 and 34 µg/day, which was about 20% of the pyrene contamination of the skin. The mean respiratory uptake of pyrene varied between 0.5 and

[8] Kroese *et al.* (2001) observed kidney, liver, skin and mammary gland tumours following administration of BaP via gavage in rats (in addition to local tumours in the digestive system).

32.2 µg/day. It was estimated that an average of 75% of the total absorbed pyrene enters the body through the skin. Therefore, dermal absorption was responsible for the main portion of pyrene intake as measured by 1-OHP excretion (van Rooij *et al.,* 1993c).

IARC (2010) expressed the growing awareness that occupational uptake of PAHs through the skin is substantial (Jongeneelen, 2001). For example, uptake of pyrene by the dermal route was estimated to account for as much as 75% of total body dose for coke-oven workers (van Rooij et al, 1993a); for creosote-impregnating workers, dermal pyrene uptake was on average 15-fold higher than the estimated respiratory uptake (van Rooij *et al.*, 1993b). Urinary levels of 1-hydroxypyrene also reflect dermal uptake and therefore should be interpreted as a measure of uptake via both inhalation and the skin. Creosote applied topically to mouse skin in vivo or human skin in short-term organ culture produced a complex pattern of aromatic DNA adducts with similar levels in both systems (Schoket *et al.*, 1988 a, b). Multiple topical treatments of mice with creosote resulted in accumulation of DNA adducts in lung tissues (Schoket *et al.*, 1988a). Extracts of soil samples from a wood-preserving waste site known to contain creosote and pentachlorophenol were topically applied to mouse skin. Aromatic DNA adducts were detected in distal organs (lung, liver, kidney and heart) as well as the skin. The anti-benzo[*a*]pyrene-7,8-diol-9,10-oxide–deoxyguanosine adduct was detected in all organs (Randerath *et al.*, 1996, 1997).

Other findings as for distal target organs were confirmed by the study of Letzel and Drexler (1998) that described an extended case series of skin tumours among German tar-refinery workers. Among the various histologies, 380 squamous-cell carcinomas, 218 basal-cell carcinomas and 182 keratoacanthomas were reported. Some cases had multiple tumours. The authors noted that the ratio of squamous- to basal-cell carcinomas was 1.7:1 in contrast to a ratio of 1:10 in the German population. Most of the tumours occurred in areas that had been in contact with the tar or tar fumes, notably the facial area, forearms and hands.

Based on current knowledge dermal exposure in humans is related with cancers in areas of first contact with the body and its effect is rather local than systemic.

Dermal exposure to PAHs and absorption through the skin may contribute to exposure of workers in aluminium plants and related carbon electrode-manufacturing (IARC 2012b) Exposures have been intensively (bio)monitored and have been shown to have decreased over time for some activities, such as in anode pre-baking plants (Benke *et al.*, 1998), but less so in anode manufacturing (Hopf *et al.*, 2009).

Van Rooij *et al.* (1992) showed that, in pot-rooms and anode pre-bake plants, dermal exposures do not always correlate with inhalation exposure. Measured levels of BaP were two-times higher on the wrists of workers in a bake-oven area, than the wrists of workers from a paste plant. However, exposure of bake-oven workers to BaP by inhalation was four times lower than for workers in the paste plant, while exposure to pyrene by both inhalation and dermal contact was higher in the paste plant.

Professional workers may be dermally exposed to CTPHT in mixtures or articles. Professional, wide-dispersive uses include paints, coatings, sealants and waterproofing materials, and use of clay pigeons. Exposure of professional workers is decreasing, as uses in coatings, paints and sealants are being phased out with suitable alternatives now available. Uses in roofing and road construction (which accounts for < 2% of sales according to CSRs submitted by registrants) are being phased-out in preference for petroleum pitch products where the PAH level is significantly lower than coal tar pitch without considerable lowering of the carbon content. Only specialised applications such as anti-kerosene coating for parking lots, airfields, taxi ways and fuel stations still use pitch emulsions (RIVM, 2008).

Similarly, some uses in heavy-duty corrosion protection and waterproof coatings are being

phased-out (e.g. ships and quays), but some remain (e.g. coating of pipelines and nuclear waste containers). This market, together with CTPHT-containing kerosene proof coatings represents ca. 2 000 tonnes of CTPHT per year according to information from the public consultation on economic impacts of inclusion of CTPHT in REACH Annex XIV as submitted by the Coal Chemicals Sector Group at CEFIC (European Chemical Industry Council).

Use as a binding agent in clay pigeons is also decreasing as manufacturers move towards more environmentally friendly products that use petroleum-based binders or none at all (RIVM 2008).

Overall, it can be concluded that dermal exposure may be significant to both local (skin) and systemic cancers in occupational settings. For local cancers from direct dermal contact with CTPHT in articles, BaP may again be chosen as the relevant indicator of exposure. Any contribution from dermal exposure to bladder cancer (and possibly lung cancer) risks is inherently accounted for in the dose-response relationships derived for bladder (and lung) cancers from epidemiological studies for air concentrations in sections 3.5.2 and 3.5.3.

3.4.2 General population

As discussed in section 4, the exposure estimation cannot be carried out with sufficient reliability for CTPHT as a result from its PBT and vPvB properties. Nevertheless, applicants for authorisation are expected to provide exposure estimates for exposure of consumers and humans via the environment with the aim to estimate health impacts.

Inhalation route

The general population may be exposed to low levels of CTPHT-derived PAHs via the environment through inhalation near point emission sources from energy production, uses in the carbon and graphite industries, and metallurgic smelting industries.

Exposure of the general population to PAHs from these uses is anticipated to be small in comparison to PAH exposures from the main exposure sources including vehicle exhaust, cigarette smoke, residential heating and industry by incomplete combustion of organic matter or in processes using charcoal or petroleum derivatives. Thus, instead of measurements, registrants used modelling to estimate exposure of humans via the environment from exposure resulting from downstream use and from the article service life. Possibly measurements at the emission source may be used in the exposure modelling provided by applicants for authorisation.

Umweltbundesamt (UBA, 2016), estimated the atmospheric emission of four PAHs, BaP, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene and indeno[1,2,3-*cd*]pyrene as approximately 191.5 tons per annum. Most of these emissions (93%) were attributed to combustion units in households and businesses, with approximately 5% coming from industrial processes, the rest from large combustion plants and traffic (less than 1%). Assuming that the fraction of 5% attributable to industrial processes comes from production and uses of Coal Tar Pitch and from other PAH-emitting industries, this value (5%) could be viewed as a reasonable worst-case estimate of the Coal Tar Pitch contribution to the total emission of PAH to the environment.

Kohoutek (2012) measured BaP concentrations in air in a residential area close to a Coal Tar Pitch distillation site in Europe over a calendar year. Average annual concentration of BaP in air was determined to be 4.02 ng/m³. Based on this average annual concentration of BaP in air of 4.02 ng/m³ and using a worst case 5% contribution from production and use of Coal Tar Pitch, a putative annual mean level of BaP in air near a local point source was estimated at 0.2 ng/m³ or 0.0002 µg/m^3.

The approach using airborne BaP as an indicator of exposure may also be taken to estimate the

risks from inhalation exposure of humans via the environment to coal tar pitch volatiles. The epidemiology data for workers may then be used to estimate lung and bladder cancer from inhalation for the general population as well. However, the uncertainties to such estimates will be considerable since the exposure routes and composition of the coal tar pitch volatiles will differ from that in the occupational settings that serve as a basis to derive a dose-response.

Dermal route

The dermal route is expected to be insignificant in an assessment of humans exposed via the environment.

There are currently no consumer uses of CTPHT and the relevance of direct dermal contact with CTPHT from the articles service life is declining. Uses of CTPHT for which the articles service life is relevant (e.g., waterproofing paints, coatings, sealants and waterproofing materials, clay pigeons) are declining due to agreed restrictions in many European countries, and the availability of petroleum-based alternatives with lower PAH content (RIVM, 2008). Uses are being restricted to specialised uses such as anti-kerosene coatings for airports and fuels stations.

Exposure of the general population through handling of clay pigeons appears to be limited as CTPHT is used as a binding agent under a coating paint (applicants to confirm).

Overall, significant exposure of the general population by the dermal route is not envisaged. For this reason, no dose-response was derived. However, applicants may use the relationship derived for dermal cancer and convert it to general population as relevant.

Oral route

The European Food Safety Agency (EFSA) adopted a scientific opinion presenting sets of 4 or 8 PAHs as indicators of the carcinogenic potency of PAHs through oral exposure (EFSA, 2008). The members of EFSA PAH4 and PAH8 are presented in Table 2. The EFSA PAH4 and PAH8 approach aims to assess risks of PAH in food, where PAHs will derive from a number of sources. The main PAH contamination of food can be attributed to heating, drying and smoking processes where combustion products come in direct contact with food or may be formed in situ (SCF, 2002; EFSA, 2008). SCF (2002) estimated a maximum daily intake of BaP from food of approximately 420 ng BaP per person, equivalent to approximately 6 ng/kg bw/day for a person weighing 70 kg.

EFSA (2008) compared dietary exposure of average and high-level consumers to BaP, PAH2, PAH4 and PAH8 respectively, and their corresponding $BMDL_{10}$ values derived from the two coal tar mixtures that were used in the carcinogenicity studies (mice fed with these coal tar mixtures) of Culp *et al.* (1998).

EFSA (2008) concluded that BaP is not a suitable indicator for the occurrence of PAHs in food. The principal reason for this conclusion was that a significant number of submitted food samples (30%) tested negative for BaP, whilst still showing high levels of other carcinogenic and genotoxic PAHs, with chrysene being most common and prominent (EFSA 2008).

CTPHT-derived PAHs in food can be anticipated to be very limited in comparison to the main sources for PAHs in food. CTPHT-derived PAH can contaminate food crops through atmospheric deposition on fruit and vegetables, where the waxy surfaces can concentrate low molecular mass PAHs via surface adsorption. PAHs are unlikely to accumulate in high water content plant tissues. Uptake by root vegetables from contaminated soil is likely to be limited due to strong adsorption of PAHs to the organic content of soils (SCF, 2002; EFSA, 2008).

PAHs accumulation occurs in marine organisms, but there is a wide range of tissue

concentrations under different conditions of environmental concentrations, exposure time, and ability to metabolise. Biomagnification has not been observed in aquatic systems and is generally not anticipated because organisms at higher trophic levels have the potential to metabolise PAHs (Meador *et al.*1995).

In invertebrates, including filter-feeding molluscs, accumulation of PAHs from particulated suspended in water correlates with the octanol/water partition coefficient (Log P, K_{ow}). In fish, the internal concentrations of different PAHs do not correlate with the K_{ow} (WHO 1998).

EFSA (2008) determined from samples that fresh fish had very little PAHs contamination, while bivalve molluscs, which do not metabolise PAHs, tended to show higher concentration (up to 15 µg/kg). This suggests that shellfish may be an important source of dietary PAHs.

A comparison of physical properties of the EFSA PAH8 entities (Table 1) suggests that these PAHs can be expected to behave fairly similar in the environment. Therefore, BaP, while not recommended by EFSA as a sole marker for PAH contamination of foods in general, may still be viewed as a pragmatic indicator of environmental food contamination by CTPHT specifically. BaP is a common component of CTPHT, is specified in the declared composition ranges in the REACH dossiers and, as discussed below, is also standard indicator for CTPHT inhalation and skin exposures. A dose-response is proposed using BaP as exposure indicator in section 3.6.2, but it should be noted that this relationship is derived from animals exposed to BaP *only* and thus will *not* account for carcinogenicity of other carcinogenic PAHs in CTPHT.

Therefore, applicants may see fit to assess the potential for food contamination using the PAH4 or PAH8 approach of EFSA, through individual exposure modelling of each of the components.

Table 2. Properties of EFSA PAH8 members (EFSA PAH4 members are in bold)

PAH8	MP (°C)	BP (°C)	Log-P	Water Sol (mg/L)	Vapour Press (mm Hg)	Henry's Law Constant
benzo[*a*]pyrene (BaP)	176.5	-	6.13	0.00162	-	4.57×10^{-7}
benz[*a*]anthracene	84	437.6	5.76	0.0094	2.1×10^{-7}	1.2×10^{-5}
benzo[*b*]fluoranthene	168	-	5.78	0.0015	5×10^{-7}	6.57×10^{-7}
benzo[*k*]fluoranthene	217	480	6.11	8.00×10^{-4}	-	5.84×10^{-7}
benzo[*ghi*]perylene	278	> 500	6.63	2.60×10^{-4}	1×10^{-10}	3.31×10^{-7}
chrysene	258.2	448	5.81	0.002	6.23×10^{-9}	5.23×10^{-6}
dibenz[*a,h*]anthracene	269.5	524	6.75	0.00249	1×10^{-10} (est)	1.23×10^{-7} (est)
indeno[1,2,3-*cd*]pyrene	163.6	536	6.70	1.90×10^{-4}	1.25×10^{-10} (e)	3.48×10^{-7}

Values taken from US National Library of Medicine chemIDplus: https://chem.nlm.nih.gov/chemidplus/

3.5 Cancer dose-response based on epidemiology

Exposure to PAHs has been linked to various cancers of the lung, skin, bladder, liver, and stomach in animal studies (Bostrom, *et al.* 2002). BaP in particular is known to induce lung tumours in mice, rats, and hamsters; skin tumours in mice; liver tumours in mice; forestomach tumours in mice and hamsters; and mammary gland tumours in rats (IARC 2012).

Human occupational exposures to BaP-containing mixtures have been associated with various cancers linked to specific activities. For example, lung cancers have been associated with coke production, paving and roofing activities. Lung and bladder tumours have been associated with coal gasification and aluminium smelting. Handling of soot has been associated with lung, skin, oesophageal and haematolymphatic cancers. Tobacco smoking is linked to lung, lip, oral cavity,

pharynx, oesophagus, larynx and bladder cancers (IARC 2012a).

Skin cancers, specifically the formation of epidermal tumours, were prevalent in coal tar distillation. The risks associated with the formation of skin tumours from deposition on the skin (and the associated dose-response) are addressed by reference to available animal data, whereas systemic cancer risks associated with dermal absorption are covered by available epidemiological data, as discussed below.

Lung, bladder and skin cancers are identified as the key cancer risk endpoints for exposure to CTPHT, these are the cancers for which data specific to CTPHT exposures exist from animal studies and industrial epidemiology. In the absence of information to assess possible overlaps of people developing lung cancer, bladder cancer and skin cancer, applicants are advised to assume these cancer risks are independent. Applicants should ensure that other cancer types are also considered at least in a qualitative manner in the risk assessment and the socio-economic analysis.

3.5.1 Epidemiology of lung and bladder cancer related to CTPHT exposure

Of the reviewed studies, the most appropriate for risk assessment of inhalation exposure to CTPHT is the meta-analysis of Armstrong *et al.* (2003, 2004). The authors selected BaP as the indicator of exposure to PAHs to derive unit relative risk values (URRs). The URRs were derived based on meta-analysis of 39 epidemiological studies on occupational exposures to PAH mixtures in which the main body of data came mainly from coke ovens, gasworks (coal gas production), and aluminium smelting (Søderberg potroom, prebake potroom, carbon plant) industries. It shall be noted that these are all industries with a predominantly male workforce. All 39 studies were critically evaluated before inclusion to the meta-analysis. The robust data based on nearly 3 000 cases were first analysed for a single effect measure (URR) from each study and subsequently analysed using standard meta-analytic methods. Content of BaP (selected as the indicator of exposure to PAHs) was monitored in the inhaled air in different occupational settings, nonetheless, the derived URRs account for overall combined exposure to PAH mixtures (not only to BaP).

Values of unit relative risk (URR) were derived as the increments in relative risk per unit cumulative exposure to BaP during 1 year. The authors used a benchmark of 100 μg/m^3 per year to express the URR and provide a scale for presenting relative cancer risk (Armstrong *et al.*, 2003 and 2004).

On average, unit relative risk (URR) predicted for lung cancer at 100 μg/m^3 BaP years was 1.20 (95% CI: 1.11-1.29) (Armstrong *et al.*, 2003 and 2004). An exposure of 100 μg /m^3 BaP years should be interpreted as equivalent to a concentration of 2.5 μg /m^3 BaP over 40 years (Armstrong *et al.*, 2004). For exposures in the coke ovens, gasworks, and aluminium industries, the authors estimated a unit relative risk of 1.17 for lung cancer at 100 μg/m^3 BaP years. For other industries such as carbon anode plants, asphalt use, and tar distilleries the evidence suggests higher risks at the same exposure levels (Armstrong *et al.* 2004).

The authors reported the following limitations: uncertainty in past exposures; differences in risk associated with one unit BaP in different industries (BaP is better indicator of lung cancer risk from PAHs within coke ovens, gasworks, and aluminium smelters rather than in other industries); less robust findings for bladder cancer risk which is largely based on two studies. In addition to these limitations, it should be noted that for only about one fourth of the cohorts (10/39) that served as a basis for the overall URR for lung cancer derived by Armstrong *et al.* (2003, 2004) actual measurements of BaP were available. For a further six cohorts proxies for BaP exposure (benzene soluble matter (BSM), total PAHs, carbon black) were available from

which exposure was estimated. For the remainder of cohorts (n = 23), the authors estimated exposures based on published exposure estimates in the same industries and other published epidemiologic studies.

Based on data from registration dossiers, CTPHT is mainly used in

- aluminium industry (formulation of anodes), and
- carbon and graphite industry (formulation of cathodes and black anodes, lining blocks and briquettes, formulation of Søderberg briquettes, formulation of ramming pastes, lining pastes).

Therefore, the most relevant industries covered by Armstrong *et al.* (2003, 2004) are the aluminium industry and carbon electrode manufacturing.

The relatively well-supported URR (lung cancer risk) derived from studies focused on aluminium industry was 1.16 (95% CI: 1.05-1.28). Two studies (out of eight) on which these URRs are based, gave significantly higher URRs: 1.85 (Mur *et al.*, 1987) and 1.31 (Spinelli *et al.*, 1991). Neither of these two studies reports quantitative data on PAH exposure.

In the meta-analysis by Armstrong *et al.*, carbon electrodes manufacturing is covered in studies from Moulin *et al.* (1989) and Donato *et al.* (2000). URRs derived based on these studies are presented in Table 3.

Table 3. Unit relative risk values (URRs) derived by Armstrong et al. (2003, 2004) based on studies from carbon electrodes manufacturing industry

	Exposure	Mean URR (lung cancer risk) at 100 µg BaP/m^3 (cumulative over 1 year)
Moulin 1989 Plant A	2.7 µg/m^3 BaP	2.82 (95% CI: 0.2 – 40.59)
Moulin 1989 Plant B	0.17 µg/m^3 BaP	0 (95% CI: 0 – over 1 000)
Donato 2000	Exposure data not reported	0.18 (95% CI: 0.01 – 5.61)

Although the industry-specific means could be interpreted as more representative of each industry, the estimates are also much less precise (Armstrong *et al.* 2004), and therefore the more robust average unit relative risk is used for deriving dose-response relationships in sections 3.5.2 and 3.5.5.

Conclusion

Despite some limitations, it can be concluded that the Armstrong *et al.* study (2003, 2004) provides a solid basis for evaluation of lung cancer risk from occupational exposure to coal-derived PAH mixtures. Armstrong *et al.* (2003, 2004) state that the URRs derived for industries other than coke ovens, gasworks, and aluminium industries are more tentative, and need careful consideration of potential biases and possible explanations. Due to limited exposure data in the underlying epidemiological studies, the mean URR for lung cancer at 100 µg BaP/m^3 years of 1.20 (95% CI: 1.11 – 1.29) derived by Armstrong *et al.* (2003, 2004) from all 39 underlying cohort studies was used in the carcinogenicity risk assessment for CTPHT. This average value across all industries analysed is recommended for prediction of cancer risk associated with exposures to CTPHT and its volatiles CTPVs (SCOEL 2016; TNO/RIVM 2008).

3.5.2 Dose-response relationship for lung cancer - Workers

For the purpose of risk assessment, it is reasonable to select the lung as the most relevant target organ for PAH-mediated cancer effects from CTPHT exposure, particularly in consideration of uses under high temperature, where inhalation is the primary exposure route. The lung is likely the first point of contact and a portal for systemic exposure. The lung is also highly metabolically active, facilitating the biotransformation of PAHs to dihydrodiol epoxides and quinones which are capable of covalent binding to DNA (WHO, 1998).

The cumulative risk of a person being registered with a malignant neoplasm can be estimated by applying sex- and age-specific incidence rates to the person years at risk derived from the numbers of survivors from a cohort based on a life table (Fitzpatrick *et al.*, 2000).

A life table shows, for a worker at each age, what the probability is that they die before their next birthday. Age-specific mortality rates are applied to a notional population, typically of 100 000. Starting at birth, the probability of dying in each period is applied to the number of people surviving to the beginning of the period, so that the initial figure slowly reduces to zero. This sort of life table is based on current age-specific death rates for each age used (Public Health Textbook, 2017). The way how to prepare or use the live table data is presented e.g. in Arias (2006). The European data needed for calculation of a specific age group or lifetime risk are: age specific death rate (M_x), probability of dying between exact ages (q_x), probability of surviving between exact ages (p_x), number left alive at given exact age (l_x), person-years lived between exact age (L_x), total person-years lived above given exact age (T_x). These data are available in the Eurostat database[9].

As the reference lifetime risk value used by Armstrong *et al.* (2003 and 2004) is relatively outdated (1997) and refers to the population of England and Wales, a more recent value was calculated within the preparation of this note based on the latest data on incidence of lung cancer from the year 2012 being available for most of the EU-28 countries. Current incidence rate of lung cancer in EU-28 reaches 84 cases per 100 000 (WHO Europe, 2017) and is only slightly different from the data on incidence (87 cases) published by GLOBOCAN (2012) which are used for the calculation of lifetime risk of cancer in this note. The number of person years at risk (7 634 413) was derived from the numbers of survivors from a cohort based on the Eurostat life table for the EU-28 men population from the year 2012 (EC Eurostat, 2017). Based on the above data it would be expected that the lifetime risk of contracting lung cancer in EU-28 is 7 018 registrations or 7.0% of men population in the EU-28 countries as presented in the following Table 3.

[9] Available at http://appsso.eurostat.ec.europa.eu/nui/submitViewTableAction.do

Table 4. Estimated risk of being diagnosed with lung cancer over a lifetime in the EU-28 – Male Population - 2012 data (GLOBOCAN 2012)

	Age group										Total
	0-14	15-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	
EU-28 population (male only)	40 522 754	81 554 114	18 789 311	18 686 823	17 498 409	15 985 689	14 774 951	11 578 553	10 086 580	16 271 462	245 748 646
Incidence of lung cancer (N)	10	995	2 160	6 639	14 056	22 854	31 232	34 180	35 350	66 187	213 663
Incidence of lung cancer per 100 000	0.02	1.22	11.50	35.53	80.33	142.97	211.38	295.20	350.47	406.77	86.94
Person years at risk	1 492 942	2 467 908	486 219	480 744	471 752	456 814	434 372	403 907	363 200	576 555	7 634 413
Registrations (N)	0	30	56	171	379	653	918	1 192	1 273	2 345	7 018

Relative risk predictions at given cumulative exposure values can be made using the formulae:

$RR_x = 1 + (URR - 1) \times x/100 = 1 + (1.20 - 1) \times x/100$ (linear model[10])

where x is cumulative exposure in µg BaP/m^3-years. Excess lifetime cancer risk (ELCR) is calculated from the relative risks at given exposure with the formula:

$ELCR = P_{ref} \times (RR_x - 1)$

where P_{ref} is cancer risk in the reference group (background risk in the unexposed target population).

[10] The formula in Armstrong *et al.* (2004) would be more precise than the linear model used here. However, at moderate to low relative risks, the log linear model is close to linear interpolation (Armstrong *et al.* 2004) and therefore simplification was considered justified. Under the linear assumption, exposure at estimated air concentrations of 1 ng/m^3 during will lead to a lifetime excess lung cancer risk of 5.6×10^{-6} (see below), whereas under the log-linear assumption the RR would be $1.20^{(0.04/100)}$ and the excess risk therefore would equal to 5.1×10^{-6}.

Using these equations, the following dose-response relationships were then calculated for:

- Continuous exposure for workers (all routes combined)
- Continuous exposure for general population (all routes combined)

Based on 8 h exposure for 5 days/week, the risk estimates are:

$RR_x = 1 + (1.20 - 1) \times x/100$

$ELCR = 0.07 \times (RR_x - 1)$

Table 5. Excess lifetime lung cancer risk estimated for workers exposed at different cumulative exposure (8 h-TWA concentrations of CTPHT for 40 years)

Cumulative exposure one year TWA BaP concentration (µg/m³)	Cumulative exposure (40 years × TWA exposure) (µg/m³)	Excess lung cancer risk in EU workers
100	4 000	5.6×10^{-1}
10	400	5.6×10^{-2}
1	40	5.6×10^{-3}
0.1	4	5.6×10^{-4}
0.01	0.4	5.6×10^{-5}
0.001	**0.04**	**5.6×10^{-6}**
0.0001	0.004	5.6×10^{-7}

Using the URR of 1.20 (Armstrong *et al.,* 2003), 40 years exposure to 1 ng/m³ will lead to a lifetime excess lung cancer risk of 5.6×10^{-6}.

Preferrably, applicants for authorisation provide personal air monitoring data for BaP. The dose-response relationship for lung cancer derived from Armstrong *et al.* (2003, 2004) inherently accounts for local effects from inhalation exposure as well as any contribution to lung cancer from systemic exposure via the dermal route. Thus, by using the Armstrong *et al.* (2003, 2004) inhalation exposure data it is implicitly assumed that the dermal exposure will be as in the occupational settings that were covered by Armstrong *et al.* (2003, 2004). This assumption inevitably introduces some uncertainties.

3.5.3 Dose-response relationship for bladder cancer - Workers

Armstrong *et al.* derived also a URR value of 1.33 (95% CI: 1.17 – 1.51) for urinary bladder cancer based on data from aluminium industries. However, the number of cases was small in most studies, and results were highly dependent on two large studies of aluminium production workers. Biases in the studies could impact the meta-analytic synthesis, in particular if consistent across studies in one industry. Armstrong *et al.* (2003) concluded that "*There was no evidence against a single URR for bladder cancer across all industries, but little evidence to positively support this either, with only aluminium smelters showing strongly positive associations. The*

average URR was slightly higher than for lung cancer but more imprecisely estimated" with weaker evidence of bladder cancer being associated with PAH exposures. Moreover, the incidence of lung cancer (14.9% in 2012 according to GLOBOCAN 2012) in males of the general population in EU-28 is more than twice that of bladder cancer (6.8% in 2012 according to GLOBOCAN 2012).

Based on these data, it would be expected that the lifetime risk of contracting bladder cancer in EU-28 is 3 252 registrations or 3.0% of men population in the EU-28 countries as presented in the following Table 5.

Table 6. Estimated risk of being diagnosed with bladder cancer over a lifetime in the EU-28 – Male Population - 2012 data (GLOBOCAN 2012)

	Age group										Total
	0-14	15-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	
EU-28 population (male only)	40 522 754	81 554 114	18 789 311	18 686 823	17 498 409	15 985 689	14 774 951	11 578 553	10 086 580	16 271 462	245 748 646
Incidence of bladder cancer (N)	16	591	692	2 274	4 667	7 817	11 366	13 644	16 330	39 796	97 193
Incidence of bladder cancer per 100 000	3.95×10^{-7}	7.25×10^{-6}	3.68×10^{-5}	1.22×10^{-4}	2.67×10^{-4}	4.89×10^{-4}	7.69×10^{-4}	1.18×10^{-3}	1.62×10^{-3}	2.45×10^{-3}	39.55
Person years at risk	1 392 942	2 467 908	486 219	480 744	471 752	456 814	434 372	403 907	363 200	576 555	7 534 413
Registrations (N)	1	18	18	59	126	223	334	476	588	1 410	3 252

With 8 h occupational exposure for 5 days/week, the risk estimates are:

$RR_x = 1 + (1.33 - 1) \times x/100$ (linear model[11])

where x is cumulative exposure in µg BaP/m^3-years. Excess lifetime cancer risk (ELCR) is calculated from the relative risks at given exposure with the formula:

$ELCR = P_{ref} \times (RR_x - 1)$

where P_{ref} is cancer risk in the reference group (background risk in the unexposed target population).

$ELCR = 0.03 \times (RR_x - 1)$

[11] The formula in Armstrong *et al.* (2004) would be more precise than the linear model used here. However, at moderate to low relative risks, the log linear model is close to linear interpolation (Armstrong *et al.* 2004) and therefore simplification was considered justified. Under the linear assumption, 1 ng/m^3 will lead to a lifetime excess bladder cancer risk of 4×10^{-6} (see below), whereas under the log-linear assumption the RR would be 1.20 (0.04/100) and the excess risk therefore would equal to 3.4×10^{-6}.

Table 7. Excess lifetime bladder cancer risk estimated for workers exposed at different cumulative exposure (8 h-TWA concentrations of CTPHT for 40 years)

Cumulative Exposure One Year TWA BaP concentration (µg/m³)	Cumulative exposure (40 years × TWA exposure) (µg/m³)	Excess bladder cancer risk in EU workers
100	4 000	4×10^{-1}
10	400	4×10^{-2}
1	40	4×10^{-3}
0.1	4	4×10^{-4}
0.01	0.4	4×10^{-5}
0.001	**0.04**	**4×10^{-6}**
0.0001	0.004	4×10^{-7}

Using the URR of 1.33 (Armstrong *et al.,* 2003), 40 years exposure to 1 ng/m³ will lead to a lifetime excess bladder cancer risk of 4×10^{-6}.

Preferrably, applicants for authorisation provide personal air monitoring data for BaP. The dose-response relationship for bladder cancer derived from Armstrong *et al.* (2003, 2004) inherently accounts for combined effects from inhalation and dermal exposure. Thus, by using the Armstrong *et al.* (2003, 2004) inhalation exposure data, it is assumed that the dermal exposure will be as in the occupational settings that were covered by Armstrong *et al.* (2003, 2004). This assumption inevitably introduces some uncertainties.

3.5.4 Biomonitoring: dose-response for lung cancer risk in workers

Biomonitoring may be used in occupational settings to estimate dermal and inhalation exposure to PAHs (Unwin *et al.*, 2006).

There appears to be general agreement that the urinary metabolite 1-OHP represents at present the best biomarker of occupational exposure to PAHs (SCOEL 2016). It should be pointed out that for evaluation of low-level occupational exposure to PAHs, it is crucial to consider intra- and inter-individual background variation in the evaluation of 1-OHP. The highest contribution to urinary occurrence of 1-OHP originates from environmental tobacco smoke, but also different country, cooking culture, and behaviour is of influence (Hansen *et al.*, 2008). Some papers, e.g. Klöslová *et al.* (2016) and Unwin *et al.* (2006) confirmed good correlation between 1-OHP in urine and BaP or total PAHs in air (see below).

1-OHP is a pyrene metabolite and is therefore an indirect marker of exposure to PAH mixtures that include BaP. The determination of BaP-specific metabolites, in particular 3-hydroxybenzo[*a*]pyrene (3-OHBaP), can provide a more representative indication of carcinogenic risk. However, because 3-OHBaP concentrations measured in the urine are between 1 000 and 10 000 times lower than 1-OHP, detection has been problematic. 1-OHP has therefore remained the most widely used target for occupational urinary biomonitoring of PAH mixtures. Recent improvements in analytical detection sensitivity have allowed a more specific determination of 3-OHBaP in the urine as an exposure marker for BaP (DFG 2012, SCOEL 2016). Correlations between airborne BaP exposure (8 h TWA) and 3-OHBaP levels in urine are therefore possible

and this method of direct BaP biomonitoring will likely become more common over time.

Urinary biomonitoring of 1-hydroxypyrene (1-OHP)

Biomonitoring of 1-OHP is based on the excretion of pyrene metabolites in urine, and therefore reflects exposure to PAH but only indirectly reflects the risk posed by systemic exposure to BaP. Nevertheless, occupational biomonitoring of urinary 1-OHP has been used extensively as a biological monitoring indicator of exposure to PAHs (Unwin *et al.*, 2006).

Due to variable exposure from smoking, food, etc., it is difficult to determine general background population levels of 1-OHP. When evaluating 1-OHP urinary excretion levels in occupationally exposed population, it is necessary to take into account also the increase of urinary 1-OHP levels during the course of a workday, reaching maximum values 3-9 h after the end of work. In addition, 1-OHP excretion levels in either pre-shift, post-shift or evening samples increase during the course of a work-week, levelling off after three consecutive days of work (Viau, 1999). It shall also be noted that, since PAHs are known to be absorbed through skin, the levels of urinary 1-OHP are particularly high in occupationally exposed populations where dermal exposure is likely (van Rooij *et al.*, 1993c; Unwin *et al.*, 2006). To aid the interpretation of biomonitoring data a detailed description is needed of the tasks carried out, the duration of tasks, and the personal protective equipment worn.

A survey published by Unwin *et al.* (2006) which involved an occupational hygiene study of 25 sites using both airborne monitoring of 17 individual PAHs and biological monitoring set the relationship between airborne BaP and urinary 1-OHP. The relationship was expressed by the authors in Figure 1.

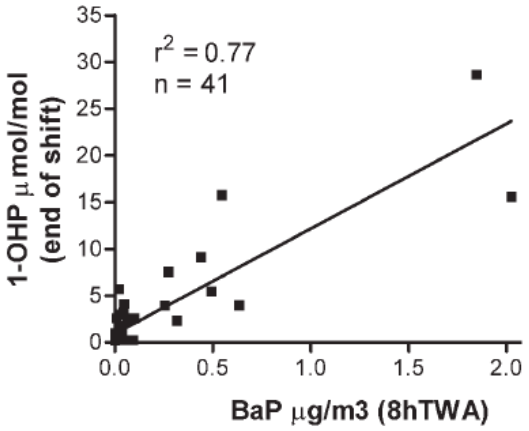

Figure 1. Relationship between BaP in air and urinary 1-OHP (y = 11.1x + 1.13) for sites without respiratory protection or significant dermal exposure (adopted from Unwin et al., 2006)

The industrial sites selected in the survey published by Unwin *et al.* (2006) involved PAHs originating from coal tar pitch, oil and bitumen, rubber fume, foundries and wood smoke. Airborne BaP correlated well (r^2 = 0.971) with levels of carcinogenic 4–6 ring PAHs and was an effective indicator of exposure for all industries where significant particle bound PAH levels were found and, in particular, for CTPV exposure. Urine samples collected from different workers at the end of shift (n = 218) and pre-shift next day (n = 213) were analysed for 1-OHP. Levels of

1-OHP in end-of-shift samples were generally higher than those in pre-shift-next-day samples and showed a good correlation (r^2 = 0.768) to airborne BaP levels if samples from workers using respiratory protection or with significant dermal exposure were excluded. Urinary 1-OHP in end-of-shift samples ranged from the limit of detection (0.5 µmol/mol creatinine) to 60 µmol/mol creatinine with a mean of 2.49 µmol/mol creatinine and a 90th percentile value of 6.7 µmol/mol creatinine. The highest 1-OHP levels were found in samples from workers impregnating timber with creosote where exposure was dominated by naphthalene. If the 11 samples from these workers were excluded from the dataset, the 90% value for end-of-shift urine samples was 4 µmol/mol creatinine (n = 207). Using the observed relationship between urinary 1-OHP and airborne BaP, a level of 1-OHP of 4 µmol/mol creatinine is roughly equivalent to an airborne BaP level of 0.26 µg/m^3.

Exposure levels in µg/m^3 can be back-calculated from urinary 1-OHP as follows:

$$concentration\ of\ airborne\ B[a]P = \frac{(\text{concentration}_{1-OHP}) - 1.13)}{11.1}$$

where the concentration of airborne BaP is in µg/m^3 and the concentration of urinary 1-OHP in µmol/mol creatinine.

Urinary biomonitoring data may be expressed as µg 1-OHP/g creatinine. To convert µg 1-OHP/g creatinine into µmol 1-OHP/mol creatinine, a factor of 1.93 can be used.

Using the back-calculated exposure levels in µg/m^3 from urinary 1-OHP and the dose-response relationship for inhalation as derived in section 3.5.2, allows to estimate the excess lung cancer risks as in Table 8. In analogy, the excess lifetime bladder cancer risk can be derived (not presented) using the dose-response relationship for inhalation from section 3.5.3.

Biological monitoring results generally represent exposure from all routes and the relationship by Unwin *et al.* (2006) was derived for sites without respiratory protection or significant dermal exposure. By using this relationship one assumes that the background exposure (including from smoking) will be similar (as in the workers in Unwin *et al.,* 2006) and that the contribution of dermal exposure to the total body burden is similar as well. This inevitably results in significant uncertainties with the derived excess lung and bladder cancer risk estimates and therefore, the relationship between airborne BaP and the urinary 1-OHP concentration from Unwin *et al.* (2006) should only be used with caution in case exposure via the dermal route is significant.

One limitation of this relationship is that it is not accurate in the low exposure range and cannot estimate exposure levels with urinary 1-OHP values below 1.13 µmol/mol (it would be negative below the corresponding air concentration).

Table 8. Excess lifetime lung cancer risk estimated for workers based on urinary 1-OHP concentrations

Urinary 1-OHP value (µmol/mol creatinine)	Converted BaP (µg/m³)	Cumulative exposure (40 years × exposure) (µg/m³)	Excess lung cancer risk in EU workers
1 000	89.988	3 599.532	5.0×10^{-1}
100	8.907	356.288	5.0×10^{-2}
10	0.799	31.964	4.5×10^{-3}
5	0.349	13.946	2.0×10^{-3}
2	0.078	3.135	4.4×10^{-4}
1.13	0.000	0.000	0.0

Urinary 1-OHP is also influenced by smoking and this should be considered in the interpretation of the urinary exposure data. The urinary 1-OHP levels are about 3-fold higher in smokers comparing with non-smokers (Huang *et al.*, 2004). The US NHANES study (Huang *et al.*, 2004) found population level of 1-OHP 0.39 (95% CI: 0.34 – 0.46) µmol/mol. The review of Jongeneelen (2001) reported 95th percentiles of creatinine adjusted urinary 1-OHP values of 0.76 µmol/mol for smokers and 0.24 µmol/mol for non-exposed population. Based on 20 samples, Kim et al. (2005) found pre-exposure mean 1-OHP concentrations of 0.20 µg/g creatinine in non-smokers and 0.51 µg/g creatinine in smokers and post-shift values of 0.39 µg/g creatinine in non-smokers and 0.73 µg/g creatinine in smokers.

Urinary biomonitoring of 3-hydroxybenzo[a]pyrene (3-OHBaP)

Recent developments in analytical detection allow a more specific determination of 3-OHBaP in the urine as an exposure marker for BaP (DFG 2012). Correlations between airborne BaP exposure (8 h TWA) and 3-OHBaP levels in urine are possible (Lafontaine *et al.* 2004, SCOEL 2016) and this method of direct BaP biomonitoring will likely become more common over time in occupational settings.

Typical urinary levels of 3-OHBaP in workers have been reported to be around 0.5 nmol/mol creatinine (Ortiz *et al.*, 2014) while the general population values vary around 0.1 nmol/mol creatinine (as published by Förster *et al.*, 2008).

Förster *et al.* (2008) studied 225 PAH-exposed employees of different industries. External exposure was determined by personal air sampling. Urinary 3OH-BaP was found in median concentrations of 0.8 ng/g creatinine and the 95th percentile of 6.7 ng/g creatinine. Regarding median concentrations, workers in coking plants showed lower 3OH-BaP concentrations (0.5 ng/g creatinine) than those employed in the production of fireproof material in refractories (1.1 ng/g creatinine), converter infeed (1.2 ng/g creatinine) and graphite electrode production (1.3 ng/g creatinine). Förster *et al.* (2008) considered that the poor correlation of BaP in the air and 3OH-BaP in urine is most probably caused by routes of uptake other than via air-for example, dermal uptake.

Lutier *et al.* (2016) analysed urinary elimination kinetic in six electrometallurgy workers after PAHs exposure. Maximum observed levels were 0.8 nmol/mol creatinine for 3-OHBaP. Urinary half-life of 3-OHBaP ranged from 4.8 h to 49.5 h. The calculation of 3-OHBaP half-life required the awareness of individual urinary background level.

Barbeau *et al.* (2014) studied 129 PAHs exposed metallurgy workers and set (based on 1-OHP/3-OHBaP ratios) the 1-OHP level corresponding to the guidance value for 3-OHBaP ranged from 0.7 to 2.4 µmol/mol creatinine. This study emphasizes to monitor urinary 3-OHBaP at the end of the last workday shift when working week exposure is relatively steady.

Zhang *et al.* (2015) study of 58 non-smokers and 81 smokers found urinary 3-OHBaP concentrations in non-smokers and smokers with 8 mg and 13 mg tar cigarettes were 1.30 ± 0.20 ng/g creatinine, 2.83 ± 1.78 ng/g creatinine, and 6.00 ± 4.44 ng/g creatinine, respectively.

Lafontaine *et al.* (2006) studied 27 smokers and 27 non-smokers without occupational and dietary exposure to PAHs. For each person, all the 24 h voided urine samples were reassembled in a single sample. Urinary 3-OHBaP ranged from < 0.01 to 0.084 nmol/mol creatinine (arithmetic mean 0.030, median 0.023) for smokers and from < 0.01 to 0.045 nmol/mol creatinine (arithmetic mean 0.014, median 0.011) for non-smokers. Considering more particularly the urinary 3-OHBaP values, the influence of smoking could be important among workers exposed to low levels of BaP (< 100 ng/m^3) and the concentrations for smokers were equivalent to most of the pre-shift values of exposed workers.

The relationship between atmospheric BaP levels and 3-OHBaP urinary concentrations was determined by Lafontaine *et al.* (2004). Atmospheric and biological monitoring was carried out on 38 people exposed to polycyclic aromatic hydrocarbons in different workplaces. Only workers with mainly respiratory exposure were included. The relationship was expressed by the authors in Figure 2.

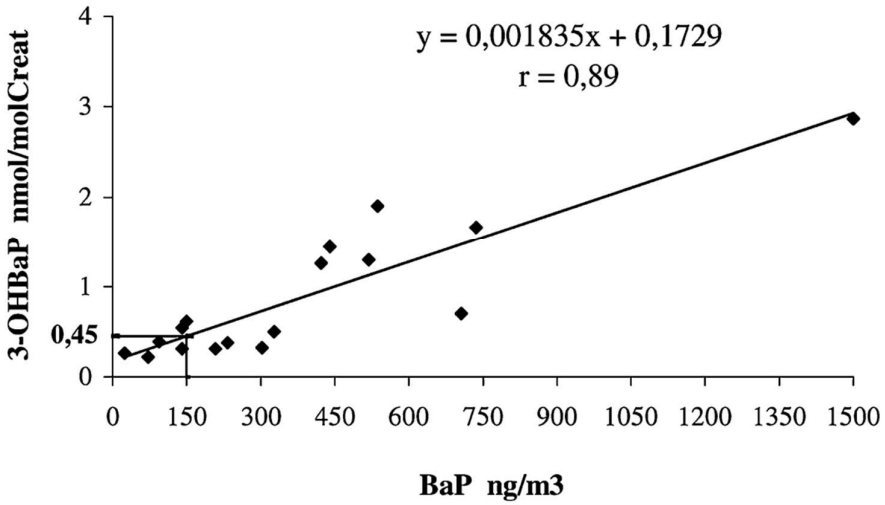

Figure 2. Relationship between atmospheric BaP and urinary 3-OHBaP (y = 0.001835x + 0.1729) (adopted from Lafontaine *et al.*, 2004)

Exposure levels in µg/m^3 can be back-calculated from urinary 3-OHBaP as follows:

$$concentration\ of\ airborne\ B[a]P = \frac{(\text{concentration}_{3-OHBaP}) - 0.1729)}{0.001835} \quad / 1\ 000$$

where the concentration of airborne BaP is in µg/m^3 and the concentration of urinary 3-OHBaP in nmol/mol creatinine.

The converted BaP in µg/m^3 from 3-OHBaP could be used afterwards into the formula for risk estimation by Armstrong *et al.* (2003).

Using the back-calculated exposure levels in µg/m^3 from urinary 3-OHBaP and the dose-response relationship for inhalation as derived in section 3.5.2, allows to estimate the excess lung cancer risks as in Table 9. In analogy, the excess lifetime bladder cancer risk can be derived (not presented) using the dose-response relationship for inhalation from section 3.5.3.

As with urinary biomonitoring uning 1-OHP, the relationship developed by Lafontaine et al. (2004) for 3-OHBaP was was also derived for workers with mainly respiratory exposure. The relationship between airborne BaP and the urinary 3-OHBaP concentration from Lafontaine et al. (2004) should therefore be used with caution in case exposure via the dermal route is significant.

One limitation of this relationship is that it is also not accurate in the low exposure range and is not able to estimate exposure levels below urinary 3-OHBaP values below 0.1729 nmol/mol creatinine (below this level, the corresponding air concentration would be negative).

Table 9. Excess lifetime lung cancer risk estimated for workers based on urinary 3-OHBaP concentrations

urinary 3-OHBaP	Converted BaP	Cumulative	Excess lung cancer

value (nmol/mol creatinine)	(µg/m³)	exposure (40 × exposure) (µg/m³)	risk in EU workers
100	54.402	2 176.068	3.0×10^{-1}
10	5.355	214.215	3.0×10^{-2}
1	0.451	18.029	2.5×10^{-3}
0.5	0.178	7.130	1.0×10^{-3}
0.2	0.015	0.591	8.3×10^{-5}
0.1729	0.000	0.000	0.0

3.5.5 Dose-response relationship for lung cancer - General population

For transforming the equations above from occupational exposure to continuous exposure of the general population, an adjustment factor of 3.03 was used to account for different conditions of exposure compared to workers:

$$\text{Adjustment factor} = 20\ m^3/d\ /\ 10\ m^3/d \times 7\ d/5\ d \times 52\ w/48\ w = 3.03$$

Using this adjustment factor for the benchmark point, this results in the following dose-response equations:

$$RR_x = 1 + 0.2 \times x \times 3.03/100$$

where x is cumulative exposure in µg BaP/m³-years. Excess lifetime cancer risk (ELCR) is calculated from the relative risks using:

$$ELCR = 0.07 \times (RR_x - 1)$$

where the lifetime risk of contracting lung cancer in EU-28 is 7 018 registrations or 7.0% of men population in the EU-28 countries as presented in Table 3.

Table 10. Excess lifetime lung cancer risk estimated for the general population exposed at different cumulative exposure (24 h concentrations of CTPHT for 70 years)

One year BaP concentration (µg/m³)	Cumulative exposure (70 years × concentration) (µg/m³)	Excess lung cancer risk in EU general population
10	700	3.0×10^{-1}
1	70	3.0×10^{-2}
0.5	35	1.5×10^{-2}
0.1	7	3.0×10^{-3}
0.05	3.5	1.5×10^{-3}
0.01	0.7	3.0×10^{-4}
0.005	0.35	1.5×10^{-4}
0.001	**0.07**	**3.0×10^{-5}**

Using the URR of 1.20, one year's exposure of 1 ng/m^3 adjusted over 70 years will therefore lead to a lifetime excess lung cancer risk of 3.0 × 10^{-5}.

Since the exposure routes and composition of the coal tar pitch volatiles will differ from that in the occupational settings that serve as a basis to derive a dose-response, the use of this dose-response relationship for the general population results in considerable uncertainties to the estimates of excess lung cancer risk.

3.5.6 Dose-response relationship for bladder cancer - General population

For transforming the equations above from occupational exposure to continuous exposure of the general population over 70 years, an adjustment factor of 3.03 was used to account for different conditions of exposure compared to workers:

$$\text{Adjustment factor} = 20\ m^3/d\ /\ 10\ m^3/d \times 7\ d/5\ d \times 52\ w/48\ w = 3.03$$

Using this adjustment factor for the benchmark point, this results in the following dose-response equations:

$$RR_x = 1 + 0.33x \times 3.03/100$$

where x is cumulative exposure in µg BaP/m^3-years. Excess lifetime cancer risk (ELCR) is calculated from the relative risks using:

$$ELCR = 0.03 \times (RR_x - 1)$$

Where lifetime risk of contracting bladder cancer in EU-28 is 3 252 registrations or 3.0% of men population in the EU-28 countries as presented in Table 5.

Table 11. Excess lifetime bladder cancer risk estimated for general population exposed at different cumulative exposure (24 h concentrations of CTPHT for 70 years)

One year BaP concentration (µg/m^3)	Cumulative exposure (70 years × concentration) (µg/m^3)	Excess bladder cancer risk in EU general population
10	700	2.1 × 10^{-1}
1	70	2.1 × 10^{-2}
0.5	35	1.1 × 10^{-2}
0.1	7	2.1 × 10^{-3}
0.05	3.5	1.1 × 10^{-3}
0.01	0.7	2.1 × 10^{-4}
0.005	0.35	1.1 × 10^{-4}
0.001	**0.07**	**2.1 × 10^{-5}**

Using the URR of 1.33, one year's exposure to 1 ng/m^3 adjusted over 70 years will therefore lead to a lifetime excess bladder cancer risk of 2.1 × 10^{-5}.

The same uncertainties mentioned above for lung cancer in the general population also apply to bladder cancer estimates using this relationship.

3.5.7 Epidemiology of other cancer types related to PAH exposure

Lung, bladder and skin cancers are identified as the key cancer risk endpoints for exposure to CTPHT, other cancer types should also be considered at least in a qualitative manner in the risk assessment and the socio-economic analysis.

The statistically significant associations between PAH exposure and specific types of cancer are collected from the Tables 2.9 – 2.17 of the IARC Monographs (IARC, 2010) and listed in Table 9 above. Statistically significant associations from additional studies, not reported in IARC (2010) are summarised in Table 10.

Limited evidence exists that PAHs may induce tumours at other sites than at the site of application, i.e., other than respiratory tract cancers after inhalation exposure or skin cancers after dermal exposure. Longitudinal study of the cohort of aluminium workers focused on total and specific mortality and incidence of 25 type/site of cancers (Spinelli *et al.*, 2006) did not confirm any statistically significant risk of PAH exposure for cancer except for stomach cancer (SIR "standardized incidence ratios") value = 1.46; 95% CI: 1.01 – 2.04) and bladder cancer (SIR value = 1.80; 95% CI: 1.45 – 2.21). Similarly, a review of cohort studies focussing on relationship between PAH and 21 cancer sites (Gibbs and Labrèche, 2014) found some significant results – mostly for lung cancer, pleura and bladder cancer.

In the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans (IARC, 2010), more than 40 case-control and case-cohort studies dealing with various cancers are discussed. Their results brought a number of point estimates indicating the relation between PAH exposure and different types of cancer, and also confirmed trends between duration of exposure and/or the amount of exposure and specific cancer. But when looking at interval estimates, lot of these results are not statistically significant (e.g. Blot *et al.*, 1983; Schoenberg *et al.*, 1987), the 95% confidence intervals are wide (e.g. Zahm *et al.*, 1989), and some of the results are based on small study samples (e.g. 3 exposed cases in the study of Grimsrud *et al.*, 1998). It does not mean that the associations do not exist.

Only 1 out of 2 studies confirmed **skin cancer** risk related with the PAH exposure from coal dust (Gallagher *et al.*, 1996). The risk detected reached OR 1.6; 95% CI: 1.0 – 2.4 and related to squamous-cell carcinoma.

Out of 7 case–control studies of kidney cancer 4 confirmed significant risk of **renal-cell carcinoma**. The highest risk but a wide confidence interval (OR 9.3; 95% CI: 1.2 – 74.2) was identified by Sharpe *et al.* (1989) and was based on 9 cases exposed in tar or pitch industry. Other significant results varied around the point estimates in the range 1.3-2.1. The later (OR 2.1; 1.0 – 4.5) was confirmed for 10 cases of substantially exposed women. The same study reported significant association between high PAH exposure and renal-cell carcinoma in men (OR 1.3, 95% CI: 1.0 – 1.6), but the relationship lost its significance and was weaker for substantially

exposed men (OR 1.2; 95% CI: 0.8 – 1.9). The highest confirmed relationship was reported by McLaughlin *et al.* (1984) and was found for exposures ≥20 years (OR 2.6; 95% CI: 1.2 – 5.7). Significant results were found also in additional case-control study of CTP exposure risk in men by Hu *et al.* (2000) - 1.4 (1.1 – 1.8).

Meta-analysis of 16 studies (Wagner *et al.*, 2015) analysing PAH exposure impact on **larynx cancer** confirmed both significant relationships; with incidence (OR 1.45, 95% CI: 1.30 – 1.62), the same as mortality (OR 1.34; 95% CI: 1.18 – 1.53). Two of the studies included in the meta-analysis were earlier mentioned in the IARC (2010) Monographs - Elci *et al.* (2003) and Becher *et al.* (2005). They found strong correlation for larynx cancer (OR 1.5, 95% CI: 1.0 – 2.2, respectively OR 6.4; 95% CI: 2.4 – 17.3 – in road construction workers).

Regarding **pancreatic cancer**, the point estimations of the three studies included into the IARC Monographs indicated relationship of the cancer with the PAH exposure, however no significant association was confirmed.

An increased risk of **stomach cancer** was observed in one out of two studies. A risk was observed in the medium category of exposure (OR 1.08; 95% CI: 1.02 – 1.15) in Cocco *et al.* (1996), but not in the low or high exposure categories. The cohort study of cancer risk in 6,423 aluminium workers in the years 1954-1997 conducted by Spinelli *et al.* (2006), based on 662 cancers tried to identify total and specific mortality and incidence for 25 cancers/sub-cancers/sites. The only significant relationship found was stomach and bladder cancer incidence (SIR 1.46 (95% CI: 1.01 – 2.04), respectively 1.80 (95% CI: 1.45 – 2.21)).

The Gustavsson *et al.* (1998) study confirmed a significant relationship between PAH exposure and **oesophageal cancer**. The risk was as twice as high than in the non-exposed group (OR 2.0; 95% CI: 1.2 – 3.5). In contrary, the study Spinelli *et al.* (2006) did not find the relationship for mortality – SMR 0.54; 95% CI: 0.20 – 1.18, nor for incidence – SIR 0.66; 95% CI: 0.26 – 1.35.

White *et al.* (2016) case-control study on PAH exposure, indoor sources and **breast cancer** found significant relationship (OR 1.45; 95% CI: 1.02 – 2.04). Nonsignificant excess of male breast cancer incidence (SIR 2.11) was reported by Spinelli *et al.* (2006).

Both case–control studies of **prostatic cancer** confirmed significant relationships with PAH exposure. Aronson *et al.* (1996) found OR 2.0; 95% CI: 1.2 – 3.5 and the study of Krstev *et al.* (1998) confirmed OR 4.0; 95% CI: 1.1 – 14.9, based on 9 cases of Afro-American power plant operators.

Some evidence was collected on **central nervous system tumours in children** in the meta-analysis of case-control studies provided by Huoi *et al.* (2014). The moderate increase of this disease was non-significantly related with paternal exposure to PAH around conception while maternal exposure did not show any increased risk. An elevated risk of childhood brain cancers has been linked to occupational paternal exposure to PAHs, with (OR = 1.6) or without (OR = 1.7) smoking. Paternal smoking alone (OR = 1.4) was also associated with the risk of astroglial tumours. However maternal occupational exposure to PAH before and during pregnancy is rare, and is not associated with childhood brain tumours (Cordier *et al.,* 2014).

Merlo *et al.* (2004) observed a significant risk of **liver cancer**, however the IARC Working Group noted that several potential causes of liver cancer, including viral infections (the rates of which are known to be high in the area), alcohol consumption and other occupational exposures may have contributed to the excess mortality from liver cancer.

Table 12. Studies with statistically significant results on different cancer risks collated in IARC Monographs on the Evaluation of Carcinogenic Risks to Humans (IARC, 2010)

Table Nr.	Title of the table	Cancer site/subtype	Nr. of studies	Nr. of studies with significant results	The highest significant risk (OR; 95% CI)	Remark	Study	Exposure
2.9	Case–control and case–cohort studies of lung cancer	lung cancer	14	5	1.9 (1.2–2.8)	meta-analysis (roofer, slater) based on 26 exposed cases	Partanen and Boffetta (1994)	Yes/no exp.; adjusted for smoking
					6.7 (4.6–9.8)	based on 857 cases, risk confirmed for heavy smokers	Nadon *et al.* (1995)	Cumulative exposure based on job description and expert judgment
					2.9 (1.2–6.7)	based on 18 cases	Grimsrud *et al.* (1998)	Yes/no exp. to PAHs
					2.1 (1.4–3.2)	101 cases (> 20 BaP–years exposure)	Brüske-Hohlfeld *et al.* (2000)	Job exposure matrix
					2.1 (1.2–3.5)	35 cases (≥ 5 µg/m^3 BaP (> 1 year))	Gustavsson *et al.* (2000)	Occup. history and expert judgment
2.10	Case–control studies of kidney cancer	renal-cell carcinoma	7	4	2.6 (1.2–5.7)	exposure ≥20 years	McLaughlin *et al.* (1984)	Based on category of occupation
					9.3 (1.2–74.2)	based on 9 cases (tar or pitch exp.)	Sharpe *et al.* (1989)	Questionnaire based
					1.7 (1.1–2.7)	based on 57 cases	Mandel *et al.* (1995)	Job classified by ISCO codes
					2.1 (1.0–4.5) 1.3 (1.0–1.6)	10 cases of substantially exposed	Pesch *et al.* (2000)	ISCO codes; job-exposure-matrix

						women; resp. 96 cases of high exposed men		
2.11	Case–control studies of urinary tract cancers	mostly bladder cancer	8	3	5.5 (1.6–19.6)	based on 9 cases (asphalt, tar exp.)	Jensen *et al.* (1988)	Interview based information
					3.1 (1.2–9.7)	46 cases (any tar exp. 8–28 years before diagnosis)	Risch *et al.* (1988)	Questionnaire based information
					1.3 (1.0–1.7)	based on 231 cases	Clavel *et al.* (1994)	Job title codes, expert. judg.
2.12	Case–control studies of skin cancers	skin cancer	2	1	1.6 (1.0–2.4)	69 cases exposed to coal dust	Gallagher *et al.* (1996)	Job category, exp. judgment
2.13	Case–control studies of laryngeal cancers	laryngeal cancer	3	2	1.5 (1.0–2.2)	based on 49 cases of highly exposed individuals	Elci *et al.* (2003)	Job exposure matrix
					6.4 (2.4–17.3)	22 cases in road construction workers	Becher *et al.* (2005)	German and ILO codes of jobs
2.14	Case–control studies of pancreatic cancer	pancreatic cancer	3	0				
2.15	Case–control studies of stomach cancer	stomach cancer	2	1	1.1 (1.0–1.1)	based on 1983 cases in medium exposure	Cocco *et al.* (2005)	Job exposure matrix
2.16	Case–control studies of oesophageal cancer	oesophageal cancer	2	1	2.0 (1.2–3.5)	based on 32 cases in low exposure	Gustavsson *et al.* (1998)	Questionnaire based; expert judgment
2.17	Case–control	prostatic cancer	2	2	2.0 (1.2–3.5)	based on 21	Aronson *et al.*	Interview based

	studies of prostatic cancer					cases in low exposure	(1996)	
					4.0 (1.1–14.9)	9 cases of Afro-American power plant operators	Krstev et (1998)	Interview based; job standard occup. codes

Table 13. Studies with statistically significant results on different cancer risks not collated in IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

	Cancer site/subtype	The highest significant risk (OR; 95% CI)	Remark	References
PAHS exposure and indoor sources	breast cancer	1.45 (1.02 – 2.04)	population-based case-control study	[2016 White]
Meta-analysis of 16 studies	larynx cancer	1.45 (1.30 – 1.62) 1.34 (1.18 – 1.53)	incidence mortality	[2015 Wagner]
16 PAHs serum levels	bladder cancer	0.79 (0.64 – 0.99)	for phenanthrene serum	[2015 Boada]
Review of cohort studies on different cancer types (out of 21)	21 cancer sites	1.0 – 2.65 1.37 – 3.02 1.3 – 4.9	lung cancer pleura, incl. mesothelioma bladder cancer	[2014 Gibbs GW, Labrèche F]
Cohort study of cancer risk for aluminium Production workers	total, specific mortality; incidence; 25 cancers	1.46 (1.01 – 2.04) 1.80 (1.45 – 2.21)	SIR for stomach ca SIR for bladder cancer	[2006 Spinelli]
Meta-analysis of 39 cohorts	lung cancer	1.20 (1.11 – 1.29)	URR for lung cancer	[2004 ARMSTRONG]
Meta-analysis of 39 cohorts	lung and bladder cancer	1.20 (1.11 – 1.29) 1.33 (1.17 – 1.51)	URR for lung cancer URR for bladder cancer risk	[2003 ARMSTRONG]
Case-control study	renal cell carcinoma	1.4 (1.1 – 1.8)	for coal tar pitch, male population	[2002 HU]

3.6 Cancer dose-response based on animal studies

3.6.1 Dose-response relationship for dermal cancer

Knafla *et al.* (2006) identified seven relevant animal studies for developing a cancer slope factor for BaP. The cancer slope factor was developed using the benchmark dose approach and the linearised multistage model. An average dermal cancer slope factor of 0.55 µg/animal/day was calculated using the upper 95th CI at the 5% effect level above background incidence as the point of departure for low-dose linear extrapolation. This cancer slope factor was then converted to a dose-equivalent slope factor of 25 mg/kg bw/day.

The studies identified in the literature and examined by Knafla *et al.* (2006) were evaluated for goodness of design (i.e., use of control groups, adequate dose spacing, clear identification of dose levels, presence of a dose-response relationship, statistically significant differences compared to controls). Those which met these criteria were selected for evaluation of their suitability for derivation of a dermal cancer slope factor that can be used to assess human risk from carcinogenic PAHs. Studies based on a two stage model of carcinogenesis (i.e., initiation–promotion) were not considered, since they typically involved application of a powerful tumour promoting agent to which humans are not typically exposed dermally in the environment, and thus complete carcinogenicity studies were preferentially used. Finally, studies that considered only a single dose in addition to the control were not considered, which also eliminated a significant portion of examined studies (Knafla *et al.,* 2006). The following Table summarises key parameters of the studies upon which the dermal cancer slope factor was derived.

Table 14. Dermal studies of BaP considered for calculation of dermal cancer slope factor (reproduced from Knafla et al., 2006)

Tested material	Mouse strain and sex	Application rate	Dosing duration	Reference
BaP and several benzo-ring derivatives of BaP	C57BL/6J (Female)	1×/2 weeks	60 weeks	Levin *et al.* (1977)
BaP, benzo[*b*]- (BbF), benzo[*j*]- (BjF), and benzo[*k*]-fluoranthene (BkF), indeno[1,2,3,-*cd*] pyrene (IP), cyclopentadieno(*cd*)pyrene (CP), and coronene (COR)	NMRI (Female)	2×/week	130 weeks (lifetime)	Habs *et al.* (1980)
Condensate from coloquint seeds (*Citrullus colocynthis*)	NMRI (Female)	2×/week	130 weeks (lifetime)	Habs *et al.* (1984)
Automobile exhaust gas condensates	NMRI (Female)	2×/week	Lifetime	Schmahl *et al.* (1977)
Extracts of soot from various sources	SENCAR (Female and Male)	1×/week	50 – 52 weeks	Nesnow *et al.* (1983)
Flue gas condensate from briquet-fired residential furnaces	CFLP (Female)	2×/week	104 weeks (lifetime)	Grimmer *et al.* (1985)
Automobile exhaust gas condensates	CFLP (Female)	2×/week	104 weeks (lifetime)	Grimmer *et al.* (1983)

Knafla *et al.* (2011) extended the earlier work to develop another dermal slope factor for BaP of 3.5 (µg BaP/cm^2/day)$^{-1}$ derived as a per-unit skin surface area, based on a mouse skin painting study of Nesnow *et al.* (1983). Another two complete carcinogenicity assay studies on mice were considered (Schmähl *et al.*, 1977; Grimmer at al., 1983), but these did not report the surface area to which BaP was applied (Knafla *et al.*, 2011).

Nesnow *et al.* (1983) studied carcinogenic risks following skin exposure of mice to samples of soot of various sources, namely coal chimney soot, coke oven materials, industrial carbon black, oil shale soot, and gasoline vehicle exhaust materials. Compositional similarity of these materials to CTPHT can hardly be determined, however, it is still regarded as relevant as these materials contain significant levels of various PAHs (reported e.g. for coke oven materials by Kirton and Crisp, 1989) which may be rapidly absorbed into the epidermis and further metabolized into reactive BaP metabolites that form stable adducts. Thus, BaP (and other PAHs) have the potential to exert carcinogenic activity in the epidermis – a portal of entry effect for dermal exposure, where the epidermis is the target tissue (Knafla *et al.*, 2011).

The available skin painting studies in mice suggest that skin metabolism of BaP leading to adduct-forming metabolites is equivalent between humans and mice. An adjustment was made for differences in epidermal thickness between humans and mice. The skin cancer slope factor was derived from studies where a mouse either exhibited a tumour or did not, a function of tumour incidence (Knafla 2011).

Using Knafla's (2011) derived cancer slope factor per unit of skin surface area of 3.5 µg BaP/cm^2/day with adjustment factor of 0.38 based on 40 year working life, 8 h/day, 5 days/week (5/7 × 48/52 × 40/70 = 0.38)[12].

ELCR = 3.5 (µg BaP/cm^2·day)$^{-1}$ × dose (µg BaP/cm^2·day) × 0.38

Table 15. Excess lifetime skin cancer (epidermal tumour) risk estimated for workers exposed at different levels of skin exposure (µg BaP/cm^2/day) of BaP for 40 years

Skin exposure (µg BaP/cm^2 /day)	Excess skin cancer risk in EU workers
1	1.3
0.1	1.3×10^{-1}
0.01	1.3×10^{-2}
0.001	1.3×10^{-3}
0.0001	1.3×10^{-4}
0.00001	1.3×10^{-5}

The uncertainties to the excess lifetime skin cancer risk can be characterised as large as a result of the interspecies extrapolation and the differences in PAH content between the test substance used in Nesnow *et al.* (1983) and CTPHT substances on the EU market. Nevertheless, the relationship may help characterise the skin cancer risks in workers from dermal exposure to CTPHT.

[12] Time scaling within a day using a factor of 8 h/24 h may not be appropriate since skin exposure may result (and be estimated from) a limited amount of contacts. BaP transferred during these contacts to the upper layers of the skin may act as a sink and be absorbed after the work shift.

3.6.2 Dose-response relationship for cancers via oral route - General population

US EPA (2017) derived an oral slope factor for BaP from a 2 year oral carcinogenicity conducted in accordance with GLP (Beland and Culp 1998 as cited in US EPA 2017; Culp et al. 1998). Female B6C3F1 mice (48/dose group) received 0, 5, 25, or 100 ppm BaP in the diet for 2 years (average daily doses: 0, 0.7, 3.3, and 16.5 mg/kg bw/day). In addition, the study included also groups of mice that received diets containing one of several concentrations of two coal tar mixtures. However, the oral slope factor was derived from the group of mice that received BaP.

US EPA (2017) derived an oral slope factor for human cancer risk of 1 per mg BaP/kg bw/day based on a BMDL10 for the tumour response in the forestomach, oesophagus, tongue and larynx of female B6C3F1 mice. This slope factor was selected as the highest (most sensitive) among the slope factors derived. US EPA (2017) considered also the forestomach tumours relevant observations for human risk assessment since humans have similar squamous epithelial tissue in the oral cavity. It is noted that other dose-related increased tumour trends were seen in animal studies that should be considered in SEA in a qualitative manner[13].

$$\textbf{ELCR} = 1\ (\text{mg BaP/kg bw/day})^{-1} \times \text{dose (mg BaP/kg bw/day)}$$

As discussed in section 3.4.2, applicants may see fit to assess the cancer risk from food contamination using the PAH4 or PAH8 approach of EFSA (2008), through individual exposure assessment of each of the components. This approach may be given preference since the relationship from US EPA (2017) was based on BaP exposure *only* and does *not* account for carcinogenicity of other PAHs in CTPHT to which humans are exposed via the environment (and thus, in this case, BaP cannot be considered an 'exposure indicator' for estimates of exposure via food consumption).

Based on the Culp *et al.* (1998) study with coal tar mixtures, EFSA (2008) derived BMDL10 values for tumour bearing animals[14] of 340 and 490 µg/kg bw/day for PAH4 and PAH8, respectively. EFSA (2008) used the lowest BMDL10 value from the different statistical models that still had an acceptable fit. With a BMDL10 relating to a 10% response level (0.1), in combination with an allometric scaling factor of 7 for mice, the following ELCR values can be derived:

$$\textbf{PAH4: ELCR} = 0.1 \times 7/340 = 2.06 \times 10^{-3} \text{ per µg/kg bw/day}$$

$$\textbf{PAH8: ELCR} = 0.1 \times 7/490 = 1.43 \times 10^{-3} \text{ per µg/kg bw/day}$$

[13] It is noted that other dose-related increased tumour trends were seen. US EPA (2017) summarised the evidence for increased tumour risk from oral BaP exposure as: "Squamous cell carcinomas or papillomas of the forestomach or oral cavity in male and female rats; squamous cell carcinomas or papillomas of the forestomach, tongue, larynx, or oesophagus in female mice; auditory canal carcinomas in male and female rats; Kidney urothelial carcinomas in male rats; jejunum/duodenum adenocarcinomas in female and male rats; hepatocellular adenomas or carcinomas in male and female rats; and squamous cell carcinomas or basal cell tumors of the skin or mammary gland in male rats."

[14] Tumours of the liver, lung, forestomach, small intestine, hemangiosarcomas, histiocytic sarcomas and sarcomas of the mesentery, forestomach, skin and kidney.

4 PBT and vPvB properties

The substance CTPHT was also included in Annex XIV of REACH for its PBT and vPvB properties because seven of the 12 PAH-constituents present in CTPHT in concentrations equal to or above 0.1% are to be considered as both vPvB and PBT substances and at least 5 to 10% of its PAH-constituents are vPvB and/or PBT[15].

According to Art 60(4), for PBT and vPvB substances, an authorisation may only be granted if it is shown that the socio-economic benefits outweigh the risk to human health or the environment arising from the use.

PBT and vPvB substances are of specific concern due to their potential to remain and accumulate in the environment over long periods of time. The effects of such accumulation are unpredictable in the long-term and practically very difficult to reverse, because an cessation of emissions will not necessarily result in a reduction in chemical concentrations in the environment. The properties of the PBT and vPvB-substances thus lead to increased uncertainty in the estimation of risk to human health and the environment. This means that, in accordance with section 4 of Annex I of REACH, hazard assessment and exposure estimation cannot be carried out with sufficient reliability.

In previous risk assessments, e.g. the restriction on decaBDE proposed by ECHA (RAC, 2014)[16], when assessing the risk of PBT and vPvB substances, RAC has taken the view that appropriate information on emissions to the environment can be regarded as a surrogate for risk. The reader is also referred to the RAC opinion on the sole application for authorisation received by ECHA for the substance HBCDD (RAC, 2015)[17].

Following the requirements under Art. 60(10) and section 6.5 of Annex I of REACH, **the applicant is advised to focus on reducing the exposures and emissions to humans and the environment to as low a level as is technically and practically possible.**

[15] According to the Agreement of the Member State Committee on Identification of Coal Tar Pitch, High Temperature as a Substance of Very High Concern According to Articles 57 and 59 of Regulation (EC) No 1907/2006, adopted on 2 December 2009.

[16] https://echa.europa.eu/documents/10162/b5ac0c91-e110-4afb-a68d-08a923b53275 - see p.16.

[17] https://ecm-dc.echa.europa.eu/dynamic-case-web/repository/2d31313037373834393531/AFA_FINALOPI_HBCDD_Use1_DN000486-43.pdf - see section 4 on exposure assessment.

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Addendum: Dose-response relationship for dermal cancer

Several companies that intend to submit applications for authorisation for the use of CTPHT expressed concern regarding the dose-response relationship for dermal cancer contained above in this note. They presented a practical example to illustrate the level of conservativeness of the dose-response relationship for dermal cancer.

The (modified) practical example is a situation where once a month a worker is exposed to a mixture containing CTPHT via a small surface of the skin (a small smear). The following can be assumed in this example:

- The mixture is a liquid containing 50 % CTPHT. Assuming a concentration of 1 % BaP in CTPHT[18], the mixture contains 5 µg BaP/mg.
- The amount of mixture on the skin is 1 mg/cm^2 skin (in comparison, this is half of the recommended application of sunscreen).
- The exposure event takes place only once per month or 12 days per year during 40 years.
- The exposed skin area is 1 cm^2.

Thus, the concentration of BaP on the skin is 1 mg mixture/cm^2 skin × 5 µg BaP/mg mixture = 5 µg BaP/cm^2. The chronic average exposure would thus be 5 µg BaP/cm^2 × 12/365 = 0.164 µg/cm^2/day. With an excess cancer risk of 1.3 per µg BaP/cm^2/day, this working life exposure situation would result in an estimated excess cancer risk of 2 × 10^{-1} (or 20 %). Clearly, this cancer risk level cannot realistically be expected in this illustrative exposure situation or where normal Occupational Health and Safety practices are applied.

Several aspects to the dose-response relationship for dermal cancer are considered:

- Knafla et al. (2011) assumed an epidermal thickness factor of **0.2** to adjust for differences in target tissue dosimetry, i.e., differences between cellular epidermal thickness between humans and mice. This factor was not included in the dose-response relationship for dermal cancer presented in Table 15.

  This adjustment factor does not account for higher thickness of the *stratum corneum* at several human skin sites, such as the palm of the hand, when compared to the dorsal skin of the mice used in the carcinogenicity study by Nesnow et al. (1983). Thus, the epidermal thickness factor does not account for possible interspecies differences in absorption related to thickness of the *stratum corneum*. However, the *stratum corneum* thickness of the inner forearm is similar to that of the mouse (Knafla et al. 2011). Moreover, the *stratum corneum* may act as a reservoir thus prolonging exposure duration, and assuming daily dosing, slower diffusion may not substantially alter the dose reaching the viable epidermis (Knafla et al. 2011).

- As indicated by Knafla et al. (2011), it can be assumed that the dermal cancer risk is proportional to the exposed skin surface area, and thus the difference in exposure area

[18] For example in the SVHC Support Document for CTPHT the BaP concentration in binder pitch and impregnation pitch is 1 %. The SVHC Support Document accessible at https://echa.europa.eu/documents/10162/73d246d4-8c2a-4150-b656-c15948bf0e77

of the mice (about 6 cm^2) and the worker (1 cm^2) should be accounted for. This means that in the above example the outcome should be multiplied by 0.17. However, in most exposure situations, the exposed skin surface will be much larger than 1 cm^2 and this correction would not help explain the conservativeness of the dose-response.

- There may be further species differences that were not corrected for in the dose-response relationship. Knafla et al. (2011) concluded that the information suggests that human and mouse skin may be similar in terms of BaP metabolism to DNA adduct forming metabolites. However, SENCAR mice are specifically selected for their sensitivity to papillomas in DMBA-TPA two stage carcinogenesis (Nesnow et al. 1983). SENCAR mice appear to be 3 to 5 times more sensitive than CD-1 mice to BaP tumour initiation (Nesnow et al. 1983). Furthermore, there appear to be increased sensitivities in SENCAR mice in the promotion phase compared to CD-1 mice (Nesnow et al. 1983). This suggests that the SENCAR mice is specifically sensitive to formation of epidermal carcinomas. The experiment from Storm et al (1990 as referenced in Knafla et al. 2011) gives some evidence of higher BaP total metabolite formation in SENCAR mice (700 pmol), and thus possibly higher adduct forming metabolites, compared with human skin (< 6 pmol).

- Knafla et al. (2011) discussed possible differences in exposure between experimental animals and humans which may be relevant in interpreting the dose-response relationship for dermal cancer. For example, the vehicle used in Nesnow et al. (1983) was acetone which may lead to drying of the skin and may compromise barrier function.

Conclusion

The dose-response relationship for dermal cancer is complex and appears to be overly conservative. Applicants may either present a well justified, refined dose-response relationship or may opt to describe dermal cancer risk in a qualitative manner.

In case of a qualitative dermal cancer assessment, applicants must provide solid and consistent justifications to support the conclusion that the operational conditions and risk management measures described in the exposure scenario respect the hierarchy of control principles (elimination – substitution – engineering methods – organisational measures – PPE) and are sufficient to avoid the likelihood of adverse health effects. It is recommended that qualitative dermal cancer assessments include exposure estimation for the dermal route as this provides a basis to evaluate the potential for exposure, and when biomonitoring data are available, dermal exposure estimates can help attributing the exposure to the different exposure routes.