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Evaluation of the health risk resulting from exposure to polycyclic aromatic hydrocarbons in coal-tar shampoo

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SUMMARY

This report discusses the safety of anti-dandruff coal-tar shampoos with respect to their contents of polycyclic aromatic hydrocarbons (PAHs). These shampoos may contain as much as 56 mg benzo(a)pyrene (BaP)/kg product. Based on a human dermal uptake study, it is plausible that BaP and other PAHs become systemically available after a single use of coal-tar shampoos. Because several PAHs, among which BaP are considered to be carcinogenic substances, the safety of these products has been questioned. The type of tumours resulting from exposure to BaP depends on the route of administration. Dermal exposure results in skin tumours, but after inhalatory or oral exposure besides to local tumour formation, systemic tumours are found as well. In this report, an estimate of external dermal exposure to BaP has been generated by application of a mathematical model. This estimate was the starting point in an assessment of the additional risk on local skin tumours after contact with a coal-tar shampoo containing 56 mg BaP/kg product. In this assessment it was assumed that this shampoo was used three times weekly. Four different risk estimates were derived, namely for contact times of 1 or 5 minutes per event and for life-time or 40 years of use. In the most optimistic scenario (1 minute of contact, 40 years of use) the additional risk on dermal tumours for BaP is 50 per 10^6 exposed people and in the most pessimistic scenario (5 minutes of contact, life-time use) the additional risk is 420 per 10^6 exposed people. In the most optimistic scenario a concentration of about 1000 μg BaP/kg product results in an additional risk on dermal tumours of 1 per 10^6 exposed people. In the most pessimistic scenario, the same risk level (1 per 10^6) is reached at about 100 μg BaP/kg product. The risk of the entire mixture of PAHs in coal-tar shampoos cannot be assessed because of lack of knowledge of carcinogenic potencies of individual PAH (exception: BaP) and variability in composition of the PAH mixture in these shampoos. In order to compensate for these uncertainties, an additional factor of 10 can be applied to the concentrations of BaP which are associated with the accepted levels of additional risk. This implicates that of the mixture of PAH in coal-tar shampoo 90% of the total carcinogenic potency of the mixture results from PAHs other than BaP. Then, BaP is considered as indicator substance for the carcinogenicity of the mixture. Thus, in the most optimistic scenario a maximal concentration of 100 μg BaP as indicator for total PAH/kg product would be advisable, while for the most pessimistic scenario a maximal concentration of 10 μg BaP as indicator for total PAH/kg product would be advisable. With respect to the systemic exposure to PAHs from coal-tar shampoos, it should be noted that the risk on systemic tumours cannot be quantified because for systemic exposure no quantitative estimate for excess cancer risk is available. Therefore, the estimates of concentrations for total PAH in coal-tar shampoos which are associated with the accepted risk level of 1 per 10^6 exposed persons may implicate an underestimation of the risk on systemic tumours.

SAMENVATTING

Dit rapport bespreekt de veiligheid van koolteershampoo met betrekking tot de aanwezigheid van polycyclische aromatische koolwaterstoffen (PAK). Deze shampoos kunnen tot 56 mg benzo(a)pyrene (BaP)/kg product bevatten. Het is aannemelijk gemaakt dat BaP en andere PAK systemisch beschikbaar komen na gebruik van koolteershampoo. Omdat verscheidene PAK, waaronder BaP worden beschouwd als carcinogene stoffen, zijn er vraagtekens gesteld bij de veiligheid van deze producten. Het type tumoren dat ontstaat na blootstelling aan BaP hangt af van de toedieningsroute. Dermale blootstelling resulteert in huidtumoren, maar na inhalatoire of orale blootstelling worden naar lokale tumoren ook systemische tumoren gevonden. In dit rapport is een schatting van de externe dermale blootstelling aan BaP afgeleid door toepassing van een mathematisch model. Deze schatting was het uitgangspunt in een beoordeling van het additionele risico op huidtumoren, na contact met een koolteershampoo waarin 56 mg BaP/kg product was verwerkt. In deze beoordeling werd aangenomen dat de shampoo drie maal per week werd gebruikt. Er werden vier verschillende risicoschattingen afgeleid, namelijk voor contacttijden van 1 of 5 minuten per keer en voor gebruik gedurende het gehele leven of voor 40 jaar. In het meest optimistische scenario (1 minuut contact, 40 jaar gebruik) is voor BaP het additionele risico 50 per 10^6 blootgestelden en in het meest pessimistisch scenario (5 minuten contact, levenslang gebruik) 420 per 10^6 blootgestelden. In het meest optimistische scenario resulteert een concentratie van ongeveer 1000 µg BaP/kg product in een additioneel risico op huidtumoren van 1 per 10^6 blootgestelden en in het meest pessimistische scenario wordt dit risiconiveau (1 per 10^6) bereikt bij een concentratie van 100 µg BaP/kg product. Het kankerrisico van het gehele mengsel van PAK in koolteershampoo kan niet precies worden vastgesteld omdat, met uitzondering van BaP, nauwkeurige kennis ontbreekt over de carcinogene potentie van de individuele PAK en omdat de samenstelling van het PAK mengsel in de shampoos kan variëren. Om voor deze onzekerheden te compenseren kan een extra factor van 10 worden toegepast op de concentratie van BaP die samenhangt met het geaccepteerde niveau van additioneel risico. Dat houdt in dat van het PAK mengsel in koolteershampoo 90% van de carcinogene potentie afkomstig is van andere PAK dan BaP. Daarmee wordt BaP beschouwd als indicator stof voor de carcinogeniteit van het gehele mengsel. Uitgaande van het meest optimistische scenario zou een maximale concentratie van 100 µg BaP als indicator voor totaal PAK/kg product raadzaam zijn, terwijl in het meest pessimistische scenario een maximale concentratie van 10 µg BaP als indicator voor totaal PAK/kg product raadzaam zou zijn. Voor de shampoo met 56 mg BaP/kg product wordt het geaccepteerde risiconiveau ver overschreden. Met betrekking tot de systemische blootstelling aan PAK uit koolteershampoo moet worden opgemerkt dat voor deze blootstelling geen maat voor het additionele kankerrisico beschikbaar is. Daarom is het niet mogelijk het risico op systemische tumoren te kwantificeren. De schatting van de concentraties aan totaal PAK die een acceptabel risico inhouden op huidtumoren zouden dus een onderschatting kunnen betekenen voor het risico op systemische tumoren.

1. INTRODUCTION

1.1 Polycyclic aromatic hydrocarbons in cosmetics

The Dutch Ministry of Public Health, Welfare and Sports commissioned the Toxicology Advisory Centre of RIVM (National Institute for Public Health and the Environment, The Netherlands) to evaluate the health risk, which might result from exposure to polycyclic aromatic hydrocarbons (PAHs) in coal-tar shampoos. These shampoos are used as anti-dandruff preparations and are available on the Dutch consumer market as non-registered products.

In a recent survey of the Dutch Consumers Association (Consumentenbond) the benzo(a)pyrene (BaP) concentration in 39 anti-dandruff shampoos (not necessarily coal-tar shampoos) was determined. One preparation contained over 30 mg BaP/kg product. Three contained between 3 and 30 mg/kg and one contained between 0.3 and 3 mg BaP/kg product. The remaining 34 were below 0.3 mg/kg (1).

In an earlier study by the Dutch Inspectorate for Health Protection (Inspectie Gezondheids bescherming; formerly: Keuringsdienst van Waren; ref. 2), 17 different coal-tar containing shampoos were analyzed for their PAH contents. Ten PAHs, among which BaP, were determined. The highest concentration determined for any of these PAHs amounted 7.7 mg/kg product for fluoranthrene. The lowest median concentration of 6 μg/kg product was found for dibenz(a,h)anthracene, while the highest median concentration of 667 μg/kg product was found for fluoranthrene. The median concentration for BaP amounted 38.5 μg/kg product with a maximum of 1186 μg/kg product.

Recently, Van Schooten et al. (3) have demonstrated that after a single application of a coal-tar containing anti-dandruff shampoo, human volunteers excreted PAH-hydroxylation products into their urine. For this particular shampoo several analytical results with respect to its BaP content are available which vary from 47.5 to 56 mg/kg product. Thus this particular shampoo contains levels of BaP which are far above the ones analyzed by Van der Schee et al. (2) or the Dutch Consumers Association (1). In appendix I, the PAH contents of a selection of 8 coal-tar shampoos, which were analyzed by Van der Schee et al. (2) are compared to the PAH contents of an anti-dandruff shampoo similar to the one studied by Van Schooten et al (3).

1.2 Aim of this report

The purpose of the present report is to provide a risk evaluation of coal-tar containing shampoos and to derive a toxicologically based limit value for PAHs in these anti-dandruff

preparations. Previously, Van Rooij (4) and ICF-Kaiser[1] (ref. 5) have have estimated the systemic exposure and took their respective estimates as starting points for the risk estimation. Van Rooij (4) followed a method which was based on urinary excretion of PAHs after use of a coal-tar shampoo ("AUC-method"). ICF-Kaiser (5) took estimates of dermal uptake constants from literature and based on these calculated dermal penetration rates of BaP. Details on their procedures are been presented in Appendix II. For several reasons the assessment of the additional risk as performed by these two groups is inadequate, e.g. because estimates of *internal* exposure were compared to estimates for excess life-time tumour risks on cancer for *external* oral, inhalatory or dermal exposure.

[1] ICF-Kaiser (Crump division) is an american consultancy bureau, which studied the health risk related to exposure to PAHs in coal-tar shampoo on behalf of Whitehall/Wyeth-Ayerst, the producer of the shampoo studied by Van Schooten et al. (3).

2. HAZARD IDENTIFICATION

It is well-known that many PAHs are carcinogenic in animals. IARC has classified the benzo(a)pyrene (BaP), as a class 2A compound: probable carcinogenic to humans; sufficient evidence for carcinogenicity in animals. Other non-linear PAHs are classified as class 2B or class 3 substances (possibly carcinogenic to humans or insufficient evidence, respectively). In contrast, linear PAHs (naphthalene, anthracene) do not seem to possess carcinogenic potency (6). The EU has classified BaP as a category 2 carcinogen, mutagen and reproductive toxic compound. The EU has classified some other PAHs as category 2 carcinogens, as well.
It is generally accepted that the carcinogenic PAHs are genotoxic. Their metabolites interact directly with DNA, which interactions result in genetic damage. Thus for these PAHs non-threshold approaches are followed in the hazard assessment (6,7).

Toxicity studies in animals have shown that the tumours which develop after exposure to BaP depend on the route of administration: after dermal application skin tumours will develop, while inhalatory exposure results in the development of tumours in the respiratory tract. Oral exposure results primarily in local tumours in the upper digestive tract (pharynx, oesophagus, and (fore)stomach). After oral administration, systemic (leukemia, lung, breast) tumours have been found as well (6).

3. DOSE-EFFECT RELATIONSHIP

3.1 Benzo(a)pyrene

Apart from the data set available for BaP, the information to estimate carcinogenic potency of PAHs is fairly incomplete. Even for BaP, despite a large amount of studies available, no full dose-effect relationship can be derived. However, from the data available, several authors have determined additional cancer risk estimates for oral, inhalatory or dermal exposure to BaP. All of these risk estimates were based on the induction of local tumours, namely upper digestive tract tumours after oral exposure, lung tumours after inhalatory exposure and skin tumours after dermal exposure to BaP.

3.1.1 oral exposure

For BaP itself, Slooff et al. (6) have derived an oral excess life-time tumour risk of 1 per 10^6 exposed people at 20 to 40 ng BaP/kg b.w./d.
US-EPA[2] has derived an oral Cancer Slope Factor for BaP. This factor amounts 7.3 per mg/kg b.w./d (8). The value represents the geometric mean of four different slope factors obtained by various modelling procedures. These four factors were derived from the combination of multiple data sets from two different reports using more than one sex and species. The value of 7.3 per mg/kg b.w/d represents the additional risk for upper digestive tract (i.e. local) tumours after oral exposure.

3.1.2 inhalatory exposure

For inhalatory exposure Slooff et al. (6) have based their additional cancer risk estimate on data from epidemiological studies. The emissions to which people were exposed resulted from combustion of coal which implicates exposures to mixtures of PAHs rather than pure compounds. Slooff et al. (6) stated that, "based on various epidemiological studies, BaP concentrations ranging from 0.002 to 0.02 ng/m^3 correspond to an additional life-time risk of 1 per 10^6 life-time exposed people. When weighing the different estimates and calculation methods in those studies, "a value of 0.01 ng BaP/m^3 (as indicator of the overall group of carcinogens in those mixtures) is probably the most appropriate value to be used in practice" (cited from ref. 6).

3.1.3 dermal exposure

Slooff et al. (6) have not derived a value for dermal exposure to PAHs. An indicative value can be estimated from data presented by Holland and Frome (9), who have described the effects of life-time exposure to BaP in acetone, when painted on skin of mice for three times a week. Based on this study, Brinkmann et al. (10) have estimated a dermal cancer risk estimate of 0.003 ng/cm^2 for life-time daily dermal exposure to BaP, which value

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[2] US-EPA = United States Environmental Protection Agency

represents an additional life-time cancer risk of 1 per 10^6. It should be noted that administration of BaP as a solute in acetone to the mouse skin may have improved dermal availability.

3.1.4 systemic exposure

Derivation of risk estimates associated with the risk for systemic tumours has not been carried out, neither by Slooff et al. (6) nor by other investigators. The absence of a cancer risk estimate for internal exposure to BaP prohibits a risk evaluation for this type of exposure.

3.2 Complex PAH mixtures

In the risk assessment by Van Rooij (4), the cancer risk estimates for dermal and oral exposure, as derived by RIVM (Sloof et al. ref 6; Brinkmann et al. ref 10), were divided by 10 to compensate for the presence of more than one carcinogenic PAH in the mixture in the coal-tar shampoo. It is well recognised that in cases of simultaneous exposure to PAHs toxicological interactions may occur. These interactions may be related to modifying action of individual PAHs on the metabolizing enzymes, thus influencing bioactivation of one-another. However, in complex mixtures a broadly additive action appears to occur (6). Slooff et al. (6) further argued that the overall carcinogenic potencies of 7 non-linear PAHs are 10 times less than the potency of BaP. Similarly, Kramers and Van der Heijden (11) have argued that "it seems reasonable to express the carcinogenicty of a PAH mixture in terms of "BaP equivalents", for instance by assuming that the total PAH-carcinogenicity would not likely exceed 10 to 20 times the actual BaP concentration". This statement was based on the consideration that mixtures of PAHs show a reasonable degree of constancy and that after administration of seven carcinogenic PAHs via various in several comparative studies, it seems that BaP is always among the most potent ones.

Coal-tar in anti-dandruff shampoos contains more than one PAH (table 1 and appendix I) Apart from BaP, the shampoo studied by Van Schooten et al. (3) contained at least 9 other PAHs. The carcinogenic potency of the PAH mixture in this example shampoo can be calculated, based on the PAH concentrations in the shampoo (table 1), which according to the producer was very similar to the one studied by Van Schooten et al. (3) and on the relative carcinogenic potencies of the individual substances mentioned in this table, an estimation of The result of this calculation are presented in table 1.

With respect to the relative potency factors for individual PAHs, it must be noted that the potencies (relative to BaP) taken from US-EPA and CAL-EPA[3] were provided by ICF-

[3] CAL-EPA: Californian Environmental Protection Agency

Kaiser[4] and could not be verified. RIVM data are overall relative potencies and taken from Slooff et al. (6). From table 1 it can be concluded that the overall potency of this particular mixture can be estimated to be 1.3 to 1.6 times as high as the value for BaP alone. Through a similar procedure ICF-Kaiser arrived at a relative carcinogenic potency of this mixture of 1.44 times the potency of BaP alone. The difference between the ICF-Kaiser value and the RIVM value (this report) originates mainly from the difference with which the carcinogenic potency of chrysene is estimated (American values: 0.001 to 0.01; Dutch value: 0.1).

When performing such a calculation, dose-additivity and equal bio-availability are assumed for all PAHs considered. Furthermore, the calculated result applies only for the specified PAH mixture. For other products, in which different mixtures of PAHs may be present, this calculated relative potency may estimate the risk incorrectly. Moreover, the data on the carcinogenic potencies of the individual substances, as presented in table 1, suggest unjustified confidence. In Slooff et al. (6) it can be seen that relative potencies of the various PAHs may differ greatly, depending on the assay used, the route of administration and consequently on organ or tissue targeted.
Based on the limited information on the composition of the PAH mixture in coal-tar shampoos which is available, in a first approach the contribution of the various carcinogenic PAHs can be calculated to result in a relative potency of about 1.6 BEQ (worst-case). However, as a number of uncertainties such as possibility of interactions and magnitude of cancer potencies has to be taken into account, as well as qualitative and quantitative variability of the PAH mixture in the shampoos, application of the correction factor of 1.6 may be inadequate with respect to the overall carcinogenic potency of these coal-tar shampoos. Therefore, in accordance with previous evaluations by RIVM (6,11) for the risk evaluation of coal-tar containing shampoos an uncertainty factor of 10 is suggested for exposure to the PAH mixture in coal-tar shampoos. Incorporation of this additional factor implicates that of the mixture of PAH in coal-tar shampoo 90% of the total carcinogenic potency of the mixture results from PAHs other than BaP. Then, BaP can be used as an indicator substance to monitor and regulate the mixture.

[4] ICF-Kaiser data were presented at a panel meeting held at the Dutch Ministry of Public Health, Welfare and Sports, July, 1995.

4. EXPOSURE ASSESSMENT

Bearing in mind that coal-tar shampoos come into contact with the skin of head and hands mainly and that PAHs have low volatility, only one relevant route of exposure namely the dermal route is applicable for this product. Thus exposure estimates for oral and inhalatory contact will not be provided.

4.1 Estimation of dermal exposure

An estimate of external exposure can be obtained with a mathematical model (CONS-EXPO; ref. 12). Because dermal uptake reduces the external concentration, dermal uptake is an element of the CONSEXPO exposure estimation procedure. Details on CONSEXPO model parameters and output have been given in Appendix II and III.

4.1.1 Assumptions

Aiming at the estimation of the average daily exposure, the following assumptions were made:

amount of shampoo used/ event: 20 g
number of events per week: 3
exposed skin area (scalp + hands): 1200 cm^2
concentration of BaP: 56 mg/kg product

4.1.2 scenarios

Three scenarios have been worked out:

1) a worst- case scenario, in which per event all of the applied BaP reaches the skin where it remains.

2) a scenario in which exposure per event lasts for 1 minute in total, during which the BaP concentration in the shampooing gradually decreases as a result of dermal uptake. The remainder of the BaP is washed away after the 1 minute exposure period.

3) a scenario similar to scenario 2 but with an exposure period of 5 minutes.

Scenarios 2 and 3 resemble the recommendation for use as specified by the manufacturer of the high-BaP example shampoo (i.e. the shampoo studied by Van Schooten et al. (3)). However, the product information leaflet does not indicate how long the shampoo should be left onto the scalp, nor does it recommend use of this shampoo for a limited period (e.g. a few weeks or months).

4.1.3 results of the scenario calculations

The worst-case scenario (1) is very straight-forward. It does not require application of the CONSEXPO model. According to this scenario the average dermal daily exposure equals

$$(56 \times 3/7 \times 20) / 1200 = 400 \text{ ng/cm}^2$$

(calculated as: concentration in product × frequency of use × amount used / exposed area)

Model input parameters for scenario 2 and 3 are given in Appendix II and III, together with additional information on the CONSEXPO-output. The calculated results have been presented in table 2.

5. RISK ASSESSMENT

According to Dutch policy it is acceptable that exposure to unavoidable constituents or contaminants in consumer products, results in an additional risk on cancer in no more than 1 out of 10^6 life-time exposed people. To get an estimate for the additional risk on cancer resulting from coal-tar constituents the exposure estimates as obtained above must be multiplied by quantitative risk estimates (cf. Unit Risk), bearing in mind relevant routes of exposure and relevant sites of effects.

5.1 Health risk associated with internal exposure; relevance regarding skin tumours

Various estimates of internal exposure to BaP from dermal application of coal-tar shampoo have been derived (see appendix II). As already mentioned in the chapter on hazard assessment, oral or inhalatory contact with PAHs can result in systemic tumours and in local tumours. However, an estimate for internal exposure to BaP with an adherent cancer risk is not available. Therefore, the tumour risk associated with the estimated levels of internal exposure cannot be calculated.

5.2 Health risk associated with oral and inhalatory exposure

As oral or inhalatory exposure to shampoo constituents (e.g. PAHs) is not expected to occur to a large extent, this part of the risk assessment will not be carried out.

5.3 Health risk associated with dermal exposure

5.3.1 Assessment by RIVM

RIVM (this report) has estimates the additional risk on skin tumours, based on estimates of daily average external dermal exposure. This estimate can be compared to the cancer risk estimate as derived by Brinkmann et al. (10) based on the report by Holland and Frome (9). This cancer risk estimate amounts to 0.003 ng/cm^2, corresponding to an additional cancer risk of 1 per 10^6 life-time exposed people, or in other words the risk for dermal exposure to BaP equals 333×10^{-3}/ng/cm^2. It should be noted that in the experiment of Holland and Frome (9) the actual exposure regimen was 3 times/week. This is the same exposure regimen as the one assumed for dermal exposure to coal-tar shampoo constituents using the CONSEXPO model (this report).

The cancer risk associated with use of coal-tar shampoo containing 56 mg BaP/kg product in an amount of 20 g/event, 3 events/week results in the additional cancer risks given in table 3. If it is assumed that the sensitivity to PAH carcinogenicity is age-independent and that the shampoo is not used in childhood, puberty and at high age an exposure period of

about 40 years would remain and all cancer risk estimates would be reduced by a factor of 40/70 = 0.57. These reduced risk estimates are also presented in table 3.

The worst-case scenario (scenario 1) produces an estimate for additional risk well above the 1 per 10^6 level, namely 130,000 per 10^6 (BaP) life-time exposed people. This scenario assumes that no wash-out occurs at all, Although this scenario is highly unlikely, it provides some insight in the maximum risk which is associated with the use anti-dandruff shampoos containing PAHs in coal-tar. The 1 minute and 5 minutes scenarios (scenarios 2 and 3) are probably fairly realistic. The risk estimates which are the results of these two scenarios are presented in table 3.

According to the 1 minute scenario, scenario 2, dermal exposure to BaP in coal-tar shampoo (56 mg BaP/kg product) poses an additional cancer risk to the consumer of 50×10^{-6} or 89×10^{-6} for 40 years or life-time use, respectively.

Scenario (3), which assumes a dermal exposure period of 5 minutes, indicates that exposure to BaP in a coal-tar shampoo containing 56 mg BaP/kg product poses an additional risk on cancer to the consumer of 240 or 420×10^{-6} for 40 years or life-time use, respectively.

Based on these risk levels calculated for this particular high-PAH coal-tar shampoo (i.e. the one containing 56 mg BaP/kg product) an estimation can be generated of the concentration of BaP at which cancer risks are at the 1 per 10^6 level. This can be done simply through division of the BaP concentration of 56 mg/kg product by the cancer risk this concentration poses.
In table 4 these concentrations are presented for scenarios 2 and 3. The most optimistic estimates results from the assumption that coal-tar shampoo is used for 40 years and that exposure per event last only for 1 minute. In that case a concentration of 1120 μg BaP/kg product corresponds to a risk level of 1 per 10^6. The least optimistic assumptions (life-time use, 5 minutes per event) indicate that a concentration of 133 μg BaP/kg product would result in 1 case of skin tumours per 10^6 consumers.

5.3.2 Assessments by Van Rooij and ICF-Kaiser

Van Rooij (4) took an estimate of the internal body load with BaP (34 ng/kg bw/d) and divided this value by the total exposed area, taking the result as an estimate of the dermal exposure. This estimate is indicative for the quantity which passed through the skin per cm^2 of the contact area and subsequently reached the systemic circulation. This quantity cannot be used to calculate the additional risk on dermal tumours.
ICF-Kaiser assumed that a risk assessment based on the total amount of BaP which was absorbed through the skin and reached the systemic circulation within the next 24 h (i.e. the 7 ng/kg b.w./day) would include the risk for dermal tumours when compared to the

US-EPA and CAL-EPA Cancer Slope Factors which were derived for oral exposure and the subsequent risk on digestive tract tumours.
Both procedures (Van Rooij (4) and ICF-Kaiser (5)) are inadequate to reach at an estimate for the additional risk of skin tumours, resulting from the use of coal-tar containing anti-dandruff shampoos[5].

[5] It cannot be excluded that BaP or PAHs in general which have reached the systemic circulation contribute to the genesis of skin tumours. As Brinkman et al (10 derived the risk level for external dermal exposure from an *in vivo* skin painting experiment, this possibility is accounted for.

6. CONCLUSION

It has been demonstrated that PAHs become systemically available after application to the skin as constituents of coal-tar containing shampoo. Based on dermal uptake models and / or actual exposure data, various authors have estimated the internal dose of BaP after application of a coal-tar containing shampoo to be in the range of 7 to 60 ng/kg b.w./d. However, toxicological data available for BaP do not permit a cancer risk evaluation for internal exposure. Thus, although it cannot be excluded that this internal exposure to PAHs may also pose a risk for the genesis of tumours, there is no means, as yet, to quantitate the additional risk. Moreover, such an evaluation would not provide insight in the risk of dermal tumours, resulting from topical application. To make a proper estimate of the risk of dermal exposure to BaP and other PAHs in coal-tar shampoo, the external dermal exposure must be determined or estimated. Subsequently, this exposure level must be compared to cancer risk estimates for dermal exposure.

RIVM (this report) has performed an assessment for external dermal exposure to PAH in a coal-tar shampoo, which contained as much as 56 mg BaP/kg product. The most realistic life-time exposure estimates for this route amounted to 0.27 or 1.26 ng BaP/cm^2 for 1 or 5 minutes exposure periods, respectively. Additional risk estimations were produced for life-time use or for 40 years of use. Assuming life-time use, concentrations for BaP, associated with 1 case of skin tumours per 10^6 consumers, range from 133 to 630 μg BaP/kg product. Assuming 40 years of use, these concentrations are increased to 233 and 1120 μg BaP/kg product. To avoid unjustified confidence and taking into account various uncertaintes (e.g. with respect to model assumptions and calculations), the concentration figures may be rounded to 100, 600, 200 or 1000 μg BaP/kg product, respectively. It should be noted that these estimates do not take into account the risk on tumours which may result from the systemic availability of BaP after dermal uptake. Although in various skin painting tests with BaP systemic tumours have not been observed (6) such a risk cannot be excluded beforehand, because administration via other routes does result in systemic tumours. Therefore, the BaP concentrations mentioned above may be an underestimation of the total tumour risk.

In coal-tar and consequently in coal-tar shampoos not only BaP is present but also several other carcinogenic PAHs. Therefore, a risk assessment for coal-tar shampoos should take into account the carcinogenicity of the entire PAH mixture. An accurate calculation of the carcinogenic potency of the PAH mixture could be carried out, if the PAH mixture in these products were constant in composition and if sufficient information with respect to the concentrations and carcinogenic potency of individual PAHs were available. The result of this calculation would then be applicable to all coal-tar containig shampoos. However, as only limited information is available, a number of uncertainties such as possibility of interactions and magnitude of cancer potencies has to be taken into account, as well as

qualitative and quantitative variability of the PAH mixture in the shampoos. Given these uncertainties it is more adequate to compensate for the presence of other carcinogenic PAHs by incorporation of an uncertainty factor than to estimate the carcinogenic potency of each individual PAH mixture. This uncertainty factor can be applied to the estimates of the BaP concentration at which the accepted maximal additional risk on dermal tumours (i.e. 1 per 10^6 life-time exposed people) is not exceeded. In concordance with earlier RIVM approaches (6,11) an uncertainty factor of 10 is suggested for this compensation. Taking this factor into account, maximal BaP concentrations in coal-tar shampoos which are indicative for exposure to the entire mixture can be calculated. These concentrations are given in the following list:

Maximum concentration of BaP in coal-tar shampoo

exposure period (minutes)	concentration (µg/kg product)			
	life-time use		40 years of use	
	BaP[1]	**BaP as indicator for total PAHs**[2]	**BaP**	**BaP as indicator for total PAHs**
1	600	60	1000	100
5	100	10	200	20

1 Values for BaP are rounded (cf table 4 and chapter 8) and represent an additional risk on dermal tumours of 1 per 10^6 exposed people; 2 Values of BaP as an indicator for total PAHs are obtained by dividing the corresponding value for BaP by an uncertainty factor of 10 (see section 5.2).

It is conceivable that for several coal-tar shampoos (e.g. see the list in appendix I), among which the one containing 56 mg BaP/kg product the risk level of 1 per 10^6 is greatly exceeded.

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Table 1: Concentrations of PAHs in a coal tar shampoo, their individual cancer potencies relative to BaP, and estimated overall relative carcinogenic potency of the mixture in this product.

Substance	concentration (mg/g)[1]	US-EPA[2]		CAL-EPA[2]		RIVM[3]		Overall; (worst -case)[4]	
		potency	BEQ[5]	potency	BEQ	potency	BEQ	potency	BEQ
Benzo(a)pyrene	0.061	1.0	0.061	1.0	0.061	1.0	0.061	1.0	0.061
Benzo(a)anthracene	0.091	0.1	0.0091	0.1	0.0091	0.1	0.0091	0.1	0.0091
Benzo(b)fluoranthrene	0.047	0.1	0.0047	0.1	0.0047	-	-	0.1	0.0047
Benzo(j)fluoranthrene	0.058	-[6]	-	0.1	0.0058	-	-	0.1	0.0058
Benzo(k)fluoranthrene	0.033	0.01	0.00033	0.01	0.00033	0.1	0.00033	0.1	0.00033
Chrysene	0.082	0.001	0.000082	0.01	0.00082	0.1	0.0082	0.1	0.0082
Dibenzo(a,h)anthracene	0.005	1.0	0.005	-	-	-	-	1.0	0.005
Indeno(1,2,3-cd)pyrene	0.021	0.1	0.0021	0.1	0.0021	0.1	0.0021	0.1	0.0021
total BEQs			0.082		0.083		0.081		0.096
Potency of specified PAH mixture (relative to BaP)[7]			1.3 ×		1.4 ×		1.3 ×		1.6 ×

1: According to the producer, these concentrations were found in a commercial preparation similar to the one applied by Van Schooten (3); 2: These data were provided by ICF-Kaiser and could not verified; 3: RIVM potencies represent overall data for all routes of administration, as provided by Slooff et al. (6); 4: worst case = highest BEQ taken from either CAL-EPA, US-EPA or RIVM; 5: BEQ= amount equivalent to BaP; 6: - = not determined; 7: relative potency calculated as total BEQs devided by BEQ for BaP.

Table 2. Dermal exposure to BaP in coal-tar containing shampoo as determined by the CONSEXPO model.[1]

scenario[2]	exposure period	Mean event concentration (μg/cm³)	daily average concentration[3] (ng/cm³)	daily average dermal exposure[4] (ng/cm²)
2	1 minute	4.273	1.29	0.27
3	5 minutes	4.003	6.03	1.26

1 The exposure is determined taking into account dermal absorption of BaP during the exposure period.
2 for explanation of scenario numbers see main text
3 mean event concentrations are average case point estimates from the probability distribution of exposures.
4 values were obtained by multiplication of the daily average concentration by 250 ml (volume of diluted shampoo solution) and division by 1200 cm^2 (exposed area).

Table 3: Estimates of additional dermal cancer risk for BaP occurring in a coal-tar shampoo containing 56 mg BaP/kg product.

scenario	BaP exposure estimate (ng/cm²)	Additional cancer risk[1] associated with life-time exposure (70 years)	Additional cancer risk[1] associated with 40 years of exposure
(2) 1 min exposure	0.27	**89**	**50**
(3) 5 min exposure	1.26	**420**	**240**

1 Cancer risk expressed as number of cases per 10^6 exposed people. Values in these columns were obtained after multiplication of the BaP exposure estimate by the risk for dermal application (333×10^{-3}/ ng/cm²) (see section 7.3.1)

Table 4: Maximum concentrations of BaP levels in coal-tar shampoos for various exposure scenarios.

exposure period (min)	Maximum concentration of BaP[1]	
	life-time use	40 years of use
1	**630**[2]	**1120**
5	**133**	**233**

1 in μg/kg product; for an additional risk of 1 case per 10^6; 2 calculated as: [BaP] / "Risk", in which [BaP] is the concentration of BaP in the example shampoo (i.e. 56 mg/kg product) and "Risk" is the risk calculated for the respective exposure scenario (see table 2)).

APPENDIX I

ai.1 Concentration of various polycyclic aromatic hydrocarbons in several coal-tar containing anti-dandruff shampoos

Substance	Anti-dandruff shampoo[1]																Substance
	1		2		3		4		5		6		7		8		"high coal-tar"[2]		
anthracene	149[3]	(5)[4]	1260	(7)	109	(5)	882	(9)	-[5]		-		-		-		-		anthracene
fluoranthene	896	(28)	5502	(30)	667	(29)	3710	(38)	4030	(32)	7676	(39)	1164	(45)	2327	(35)	-		fluoranthene
pyrene	745	(23)	3832	(21)	536	(23)	2887	(30)	3300	(26)	3783	(19)	465	(18)	1414	(21)	310000[6]	(48)	pyrene
benz(a)anthracene	349	(11)	1785	(10)	225	(10)	717	(7)	1690	(13)	2638	(13)	276	(11)	930	(14)	91000	(14)	benz(a)anthracene
chrysene	328	(10)	1594	(9)	211	(9)	530	(5)	774	(6)	1172	(6)	174	(7)	566	(9)	82000	(13)	chrysene
benz(b)fluoranthrene	238	(7)	1225	(7)	166	(7)	325	(3)	723	(6)	1073	(5)	145	(6)	315	(5)	47000	(7)	benz(b)fluoranthene
benz(k)fluoranthrene	104	(3)	604	(3)	76	(3)	158	(2)	465	(4)	722	(4)	79	(3)	247	(4)	33000	(5)	benz(k)fluoranthene
benz(a)pyrene	219	(7)	1141	(6)	150	(7)	267	(3)	773	(6)	1186	(6)	137	(5)	449	(7)	61000	(9)	benz(a)pyrene
dibenz(ah)anthracene	6	(0)	65	(0)	13	(1)	20	(0)	533	(4)	813	(4)	10	(0)	45	(1)	5000	(1)	dibenz(ah)anthracene
benz(ghi)perylene	91	(3)	614	(3)	68	(3)	110	(1)	193	(2)	316	(2)	54	(2)	153	(2)	-		benz(ghi)perylene
indenopyrene	94	(3)	710	(4)	71	(3)	117	(1)	223	(2)	375	(2)	55	(2)	164	(2)	21000	(3)	indenopyrene
benz(j)fluoranthrene	-		-		-		-		-		-		-		-		58000	9	benz(j)fluoranthrene
total analyzed PAHs	3219	(100)	18332	(100)	2292	(100)	9723	(100)	12704	(100)	19754	(100)	2559	(100)	6610	(100)	650000	(100)	total analyzed PAHs

1 data for shampoo 1-8 are taken from Van der Schee et al. (1). From 17 analyzed shampoos, only 8 were selected with comparatively high total PAH concentrations; 2 this shampoo is similar to the example shampoo for which in this report a risk assessment has been carried out; 3 concentrations are given in µg/kg product; 4 numbers between parenthesis are percentages of total analysezed PAHs; 5 - means not analyzed; 6 the pyrene contents of this shampoo has been estimated on the basis of analytical results provided by Van Rooij (2). The concentrations of the other PAHs were provided by ICF-Kaiser (3).

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3. ICF-Kaiser data were presented at a panel meeting held at the Dutch Ministry of Public Health, Welfare and Sports, July, 1995.

APPENDIX II

aii.1 estimation of internal exposure

In this appendix three ways are described to estimate the internal exposure to BaP. Van Rooij (1) followed a method which was based on urinary excretion of PAHs after use of a coal-tar shampoo ("AUC-method"). ICF-Kaiser (2) took estimates of dermal uptake constants from literature calculated dermal penetration rates of BaP. RIVM (this report) estimated sytemic exposure using a mathematical model. In the following text these three methods and their results are compared.

aii.1.1 Van Rooij approach:

The exposure to BaP in coal-tar shampoo can be estimated from the Van Schooten paper (3). For this study human volunteers washed their hairs twice with coal-tar shampoo for 30 seconds. It was shown that the particular shampoo contained 285 mg pyrene and, probably among other PAHs, 56 mg of BaP/kg product. In total 20 g of shampoo was used. Over the next two days following the exposure, 1-hydroxypyrene (1-OH-pyrene), a metabolite of the coal-tar constituent pyrene, was excreted into the urine.

From the time-course of the 1-OH-pyrene excretion in the urine, Van Rooij (1) derived an estimate of the total internal exposure to BaP. Firstly, an estimate of the total internal exposure to pyrene was made. Based on a renal excretion rate estimate for 1-OH-pyrene, an estimate for the total amount of 1-OH-pyrene formed from pyrene was obtained. Based on an estimate of the biotransformation efficiency of pyrene into 1-OH-pyrene an estimate of the total systemic load to pyrene was found.

Secondly, assuming equal efficiency for dermal passage of pyrene and BaP the total amount of BaP absorbed from the coal-tar shampoo was calculated from the concentration ratio of pyrene over BaP in the product.

Van Rooij (1) reached the conclusion that under the conditions the shampoo was used and applying average assumptions for biotransformation and excretion rates (see table 1 to this appendix), the internal body load to BaP was 34 ng/kg b.w./day. This value indicates that from the amount of BaP applied (560 µg/d), approximately 0.43% was absorbed through the skin.

The estimation of urinary excretion of 1-OH-pyrene was based on *in vivo* data, while other input data in this procedure are assumptions. However, a number of these can be substantiated by data from scientific literature. One of the key assumptions in the Van Rooij (1) approach is that pyrene and BaP are more or less equally effective in penetrating the skin. This view is supported by experimental data (cf. various papers cited in ref. 4). Further more, taking into account the physico-chemical characteristics of the two substances and all other uncertainties in the procedure, this assumption is defendable and will not lead to major under- or overestimation of internal body load.

aii.1.2 ICF-Kaiser approach:
Alternatively, estimates of internal exposure may also be obtained from experimentally determined absorption factors. This approach has been followed by ICF-Kaiser (2). Based on an skin penetration study by Wester et al. (5), ICF-Kaiser assumed that absorption from a single coal-tar shampoo application with a contact time of 1 minute is about 0.017% of the amount of total PAHs applied. To their opinion the internal body load to BaP amounts to 7 ng/kg b.w./event.

The estimation of ICF-Kaiser (7 ng/kg b.w./day) is about 5 times less than the Van Rooij estimate (34 ng/kg b.w./day). The crucial point in the ICF-Kaiser approach is the assumption that dermal absorption in an *in vitro* experiment is similar to that in the situation of daily life. It should be noted that in monkey skin, in an *in vivo* situation, a dermal absorption twice as high as *in vitro* was found in the paper of Wester et al. (5), the starting point for the ICF-Kaiser calculations. Furthermore, the calculation of the dermal uptake by ICF-Kaiser was performed for an amount of shampoo about 1/3 of that applied in the Van Schooten study, which was the starting point for the Van Rooij report.

aii.1.3 RIVM approach:
A third way to estimate the amount of BaP which reaches the circulation after dermal application is by application of a mathematical model. Such an exercise has been performed with the newly developed mathematical model CONSEXPO (6). In CONSEXPO, dermal diffusion constants were estimated with various theoretical models resulting in a range of values from which CONSEXPO constructed a probability distribution of internal exposure, via Monte-Carlo sampling from a uniformly distributed probability distribution.

Assuming use 20 g of coal-tar shampoo 3 times a week for 60 seconds per event, this model calculated an average daily untake of 51.2 ng/kg b.w. with a 95-percentile of 129 ng/kg b.w. (scenario 2 as mentioned in the main text). With CONSEXPO, the internal and external exposure resulting from a 5 minutes contact period were calculated as well (scenario 3 in the main text).

Other exposure and model parameters are given in table aii-1 to this appendix and the results of the CONSEXPO model are presented in appendix III. The results of the CONSEXPO model for scenario 2 compare well with the estimates as produced by Van Rooij (1).

aii.1.4 Conclusion

Taking the differences between the three approaches and the different use scenarios into account, the three approaches to estimate internal exposure to BaP corroborate one another.

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Table aii-1. Scenario parameters for the estimation of exposure to PAH in coal-tar shampoos as assumed by Van Rooij and by RIVM.

parameter	scenarios	
	Van Rooij[1]	RIVM[1]
amount of product used (g/d)	10	20
contact time	60 s	60 or 300 s
frequency	daily	3/week
exposed area (scalp + hands; cm^2)	1200	1200
BaP concentration (mg/kg)	56	56
washing water (ml)	250	250
Log K_{ow} for BaP	6.4	
molecular weight BaP	252	252
Body weight (kg)	70	uniformly distributed from 50 to 70
measured amount of 1-OH-pyrene (nmol) excreted after use of 20 g of shampoo	30.9	
background excretion of 1-OH-pyrene (nmol/	2.3	
conversion factor pyrene to 1-OH-pyrene	0.75	
fraction of 1-OH-pyrene excreted into urine	0.5	
Ratio BaP/pyrene in shampoo	0.25	
Log partition coefficient BaP product/blood		uniformly distributed from 1.5 to 10
Skin permeability BaP (cm/min)		uniformly distributed from 0.01 to 100

1 Van Rooij: see ref. 1 and RIVM: this report

APPENDIX III

aiii.1 CONSEXPO model (version 1.03) output data for exposure to BaP in coal-tar shampoo.

aiii.1.1 comments

Uptake is determined using a physiological dermal diffusion uptake model based on Fick's law. Estimates of exposure are given as average case and cumulative worst-case values, because body weight and dermal diffusion coefficient were determined by Monte Carlo procedure from uniformly distributed parameters. Note that "worst-case" applies to the calculation of *uptake* estimates, which is why average case dermal exposure estimates (*external*) are higher than worst-case exposure estimates.

aiii.1.2 data

Compound: benzo(a)pyrene (CAS: 50-32-8)
Subject: person ; weight: 50.000 - 70.000 kg, uniform distribution

Parameters for exposure estimates:
Product amount: 20 g
Product volume: 20 cm^3
Weight fraction of compound: 5.60e-05 fraction
(<=> 56 mg/kg)
Dilution before use: 12.5 times
Frequency of contact: 3/week

Parameters for uptake estimates:
Model: diffusion model
Contact area: 1200 cm^2
Blood volume at contact area: 120 cm^3
Blood flow at contact area: 25.8 cm^3/min
Partition coefficient product/blood: 1500 - 10000 dimless, uniform distribution
Skin permeability: 0.01 - 100 cm/min; uniform distribution

SCENARIO	2	3
CONTACT parameters		
Duration of contact per event (minutes)	1	5
Duration of actual use per event (minutes)	1	5
DERMAL exposure (external)		
Mean event concentration (average case; $\mu g/cm^3$)	4.273	4.003
Daily average (average case; ng/cm^3)	1.287	6.027
Mean event concentration (cumulative worst-case; $\mu g/cm^3$)	3.959	3.320
Daily average (cumulative worst-case; ng/cm^3)	1.192	4.999
UPTAKE (systemic exposure)		
Average case estimate (ng/kd.day)	51.2	83.6
Cumulative worst case estimate (ng/kg.day)	129	196