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Cancer risk assessment of azo dyes and aromatic amines from tattoo bands, folders of paper, toys, bed clothes, watch straps and ink

M.J. Zeilmaker, H.J. van Kranen, M.P. van Veen and J.A. Janus

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RIVM, P.O. Box 1, 3720 BA Bilthoven, telephone: 31 - 30 - 274 91 11; telefax: 31 - 30 - 274 29 71

Abstract

A quantitative assessment was performed to estimate the cancer risk of individuals using tattoo bands, folders of paper, toys, bed clothes, watch straps and ink which are colored with azo dyes. In the mentioned products benzidine, *o*-anisidine, 2,4-toluenediamine, 4,4'-diaminodifenylmethane, 3,3'-dichlorobenzidine en *o*-toluidine were found. The risk assessment compares the (estimated) level of carcinogenic aromatic amines which, during the period in which products are used, enters the body and the acceptable limits, as set for the chronic exposure to these amines. The following aspects were taken into account in the risk assessment: the probability that products contain aromatic amines, the frequency with which products are used, the amount of amines in products, the migration of amines from products, the absorption of migrated amines through the skin or in the lungs and the acceptable limits as set for the chronic exposure to aromatic amines. The latter limits were set equal to the "Negligible Risk Level"-NRL (life-long exposure leading to one extra case of cancer in one million exposed persons) and the "Maximal Permissible Risk Level-MPRL (lifelong exposure leading to one extra case of cancer in ten thousand exposed persons).

In deriving NRLs and MPRLs two approaches were followed. In the first approach NRLs/MPRLs were derived from epidemiological data. In the second, traditional, approach NRLs/MPRLs of benzidine related amines were derived from animal data. When the first approach was taken all calculated cancer risks exceeded the NRL, with risks ranging from $1 \cdot 10^{-6}$ to $9000 \cdot 10^{-6}$. In three products this risk even exceeded the MPRL. When the traditional approach was taken the calculated cancer risks exceeded the NRL in only two products.

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Samenvatting

Dit rapport beschrijft een schatting voor het risico op kanker dat verbonden is aan het gebruik van tatoe bandjes, vouwblaadjes voor kinderen, textiel speelgoed, beddegoed (lakens), horlogebandjes en inkt waarin kankerverwekkende aromatische aminen uit azokleurstoffen voorkomen. In deze producten zijn benzidine, *o*-anisidine, 2,4-toluenediamine, 4,4'-diaminodifenylmethaan, 3,3'-dichloorbenzidine en *o*-toluidine aangetroffen.

In de risicoschatting worden de (geschatte) hoeveelheden aromatische kankerverwekkende aminen die tijdens het gebruik van genoemde producten in het lichaam opgenomen kunnen worden vergeleken met het levenslange acceptabel geachte blootstellingsniveau van deze aminen. Dit niveau is gesteld op de blootstelling die leidt tot 1 extra geval van kanker per miljoen levenslang blootgestelden ("Negligible Risk Level", NRL) resp. 1 extra geval van kanker per tienduizend levenslang blootgestelden ("Maximum Permissible Risk Level", MPRL).

De NRL/MPRL van benzidine werd uit epidemiologisch onderzoek afgeleid. Voor benzidine verwante aminen is dergelijk onderzoek niet voorhanden. NRLs/MPRLs van deze verbindingen zijn als volgt verkregen. Allereerst werd verondersteld dat de mens, net als vermoed wordt voor benzidine, veel gevoeliger is voor de carcinogene werking van aromatische aminen dan proefdieren. Gegeven deze veronderstelling werden NRLs/MPRLs berekend door de NRL/MPRL van benzidine te corrigeren voor verschillen in carcinogeen vermogen zoals bekend voor aromatische aminen. Deze benadering leidt tot relatief lage acceptabele blootstellingsniveaus, en dientengevolge hoge risico's op kanker, zeker wanneer zij vergeleken wordt met de meer traditionele manier om NRLs/MPRLs te berekenen, d.w.z. door extrapolatie van carcinogeniteit van proefdieren naar de mens. Om dit laatste effect te kunnen beoordelen zijn voor aan benzidine verwante aminen risico's op kanker ook berekend op basis van gegevens uit proefdieronderzoek.

Wanneer epidemiologisch onderzoek over de carcinogeniteit van benzidine als uitgangspunt genomen werd voor het berekenen van NRLs/MPRLs bleek het gebruik van alle onderzochte producten te leiden tot een blootstelling aan aminen die leidt tot een risico dat gelijk of hoger is dan de NRL. Voor drie producten bleek deze blootstelling zelfs een risico boven de MPRL te geven.

Wanneer NRLs/MPRLs van aan benzidine verwante aminen berekend werden op basis van proefdieronderzoek bleek dat voor slechts twee producten de NRL overschreden werd.

Om tot een meer realistische risicoschatting te komen is nader onderzoek nodig naar een verbeterde blootstellingsschatting en risicokarakterisering van aromatische aminen.

Summary

This report describes a cancer risk assessment for individuals using tattoo bands, children's folders of paper, textile toys, bed clothes (sheets), watch straps and ink which contain carcinogenic aromatic amines from azo dyes. In these products benzidine, *o*-anisidine, 2,4-toluenediamine, 4,4'-diaminodifenylmethane, 3,3'-dichlorobenzidine and *o*-toluidine were detected.

In the risk assessment the (estimated) amount of carcinogenic aromatic amines which, during the period in which products are used, enters the body is compared with the acceptable limit as set for the chronic exposure to these amines. For the latter limit the "Negligible Risk Level" (NRL), i.e. the (assumed) life-long exposure which leads to 1 extra case of cancer in one million life-long exposed persons, and the "Maximal Permissible Risk Level" (MPRL), i.e. the lifelong exposure which leads to 1 extra case of cancer in ten thousand life-long exposed persons, were taken.

The NRL/MPRL of benzidine was obtained from human epidemiological data. For benzidine related amines human data are lacking. NRLs/MPRLs of these amines were obtained as follows. Firstly, the indications that, as in the case of benzidine, humans are much more sensitive for the carcinogenic action of aromatic amines than animals were assumed to hold for benzidine related amines as well. Given this assumption NRLs/MPRLs were then calculated by correcting the NRL/MPRL of benzidine for differences in carcinogenic potency as known for aromatic amines. The consequence of using this approach is that it leads to relative low acceptable exposure levels, and hence relative high cancer risks, when compared with the traditional way of deriving NRLs/MPRLs in the absence of human data, i.e. by extrapolation of carcinogenicity data from animals to man. To evaluate the latter effect risk estimates of benzidine related amines were therefore also calculated with NRLs/MPRLs derived from animal carcinogenicity data.

When human carcinogenicity data of benzidine were used as the base for the calculation of NRLs/MRPLs the use of all products examined leads to an exposure of amines creating a risk equal to or exceeding the NRL. For three products the calculated risks even exceeded the MPRL.

When the acceptable exposure level of benzidine related amines were obtained from animal data, the use of only two products would lead to a cancer risk which exceeds the NRL.

In order to arrive at a more realistic risk assessment, research on an improved exposure assessment and hazard identification of aromatic amines is recommended.

1. Introduction

Azo dyes are a diverse and widely used group of organic dyes which represent a wide spectrum of colours and can be used for a variety of materials, including textile, leather, paper and plastic. Azo dyes all have one or more azo-groups (-N=N- group). Under certain conditions, reductive cleavage of the -N=N- bond may occur, resulting in the split off of the primary aromatic amine(s) used in the synthesis of the dye. A number of these aromatic amines, e.g. benzidine, have been classified as human or animal carcinogen and the azo dyes based on these amines are considered to be carcinogenic as well.

In 1995 the results of a survey conducted by the Inspectorate for Health Protection showed the presence of benzidine-based azo dyes and other azo dyes in garments and other textiles sold in the Netherlands (Van Haperen and Hiemstra, 1995). This finding prompted the Ministry of Welfare, Health and Sports to ask the National Institute of Public Health and the Environment (RIVM) to perform a risk assessment for consumers dermally exposed to azo dyes from garment (specifically underwear was chosen because this garment is worn directly on the skin). The risk assessment showed that the acceptable risk level for benzidine with respect to carcinogenicity is exceeded by wearing underwear colored with a benzidine-based azo dye (Speijers *et al.,* 1996). Based on this finding the Dutch government has banned the trade in clothing, footwear and bedclothes which contain azo dyes (Commodities Act Decree[1]). The ban comprises all azo dyes that can split off one of twenty primary amines specified in the decree.

Furthermore, a survey by the Inspectorate of Environmental Hygiene carried out in 1994/1995 revealed that azo dyes not only enter the Netherlands in various consumer products, but a number of these dyes themselves are imported, applied and traded in the Netherlands (Klingenberg *et al.*, 1997, as cited in Mensink *et al.,* 1997). This survey did not provide, however, detailed information on the use of azo dyes in the Netherlands, nor on the occurrence of azo dyes in consumer products. For this reason, the Ministry of Housing, Spacial Planning and Environment ordered a broad study on the presence of azo dyes in consumer products (with special regard to products which are not regulated in the Commodities Act) and on the regulations on azo dyes in other countries. In this study, conducted in 1997 by Consultancy and Research for Environmental Management (CREM), a screening of relevant product-dye combinations was made from the data on possible applications, actual concentrations in products (using a large data base of test results from the Netherlands and Germany), potential exposure (degree of contact) and the existing regulatory legislation. The results of this study (Mensink *et al.* 1997; 1998) showed that, in addition to garment and footwear, other textile and leather products such as toys, household textiles, carpets and leather watch straps may need further attention with respect to cancer risk, as well

[1] The final "Commodities Act Decree Azo dyes" (In Dutch: *Warenwetbesluit Azo-kleurstoffen*, published in the official State Journal *Staatsblad 339, 1998)* was preceded by the temporary "Commodities Act Regulation Azo dyes" (In Dutch: *Warenwetregeling Azo-kleurstoffen*, published in the official state journal *Staatscourant 143, 29 july 1996).*

as a number of products of other materials, including paper products, cosmetics, shoe polish, and ink and paints.

Following the CREM study, the Ministry of Housing, Spatial Planning and Environment asked RIVM to perform cancer risk assessments on a number of the above-mentioned consumer products. Firstly, a risk assessment on several kinds of garments and footwear was made. These risk assessments showed that in all of the studied cases (garment: six pieces; footwear: four pieces) the wearing of garment and footwear may lead to an exposure to amines that exceeds the acceptable risk level with respect to carcinogenicity (Zeilmaker *et al.*, 1999; see also the discussion in the present report) when acceptable risk levels derived from human data on benzidine were used, but extrapolation from animal data produced a different picture. Secondly, in the present report risk assessments on other products, viz. tattoo bands, folders of paper, textile toys, bedclothes, watchstraps and ink are presented. Except for bedclothes these products are not included in the Commodity Act Decree. The amines detected in the products included in the present report are benzidine (CAS No. 92-87-5), *o*-anisidine (CAS No. 90-04-0), 2,4-toluenediamine (CAS No. 95-80-7), 4,4'-diaminodifenylmethane (CAS No. 101-77-9), 3,3'-dichlorobenzidine (CAS No. 91-94-1) and *o*-toluidine (CAS No. 95-53-4).

The European Union is currently preparing a directive to ban the use of azo dyes in a number of consumer products and the trade of these products, largely based on the existing product-specific legislation already adopted in some of the EU member states (Germany, France, the Netherlands). The draft EU directive, focused on textile and leather products which have the potential of coming into direct and prolonged contact with the human skin or oral cavity, includes the following consumer products (EU, 1999)[2]:
- clothing, bedding, towels, hairpieces, wigs, hats, nappies and other sanitary items,
- footwear, gloves, wristwatch straps, handbags, purses/wallets, briefcases, chair covers,
- textile or leather toys and toys which included textile or leather garments,
- carpets.

The EU directive, which has to be implemented in the national legislation of all EU members states within one year after the final directive will be in force, applies to all azo dyes that may release one or more of the twenty one aromatic amines specified in the directive (viz. the twenty amines from the Dutch and German regulation and, additionally, *o*-anisidine).
In the Netherlands and other European countries there are some additional national or EU regulations that limit or prohibit the use of carcinogenic amines (especially benzidine, 2-naphtylamine and 4-aminobiphenyl, which have been classified as human carcinogen) and azo dyes in consumer products. These regulations include foodstuffs, food packaging materials, cosmetics, and substances and preparations sold to the public. For detailed data, see Mensink *et al.* (1997).

[2] These products are mentioned specifically in the draft directive, but the directive also applies to other (textile and leather) products that may release the aromatic amines in concentrations above 30 ppm (EU, 1999). The 30 ppm limit for the free amines is also used in the Dutch Commodities Act Decree.

The CREM study and the present RIVM study aim at providing information which can be used to decide whether or not the current national policy measures and the forthcoming international (EU) policy measures for azo dyes in consumer products are sufficiently protective with respect to human cancer risks.

2. Exposure Assessment

2.1 Used data base

Mensink *et al.* (1997) gives a broad overview of consumer products in which carcinogenic. aromatic amines are found. This database was taken as the starting point for the risk assessment presented in this report.

In Mensink *et al.* (1997) the following products are mentioned to contain carcinogenic amines: carpets, household textiles and towels, bed clothes, "accessoires", "baby accessoires", watch straps, "toys", shoe-polish, ink ("airbrush") and textile paint. To assess the cancer risk associated with these products at least information on the type of the product (to assess the characteristics of the use of the product) and the amount of the carcinogenic amine which is present in the product (to assess the uptake of the amine from the product) needs to be known. When the products mentioned before were screened on these criteria the following result was obtained.

For "accessoires", "baby accessoires", "toys" (characteristics of use not to be determined), shoe-polish, and textile paints (amount of amine unknown) the necessary information is not available.

In household textiles the amount of 2,4-toluenediamine was reported to range from 30 to 2700 ppm (mg/kg). In towels a range of 30 to 1500 ppm was reported for benzidine. When used household textiles and towels come into contact with the skin. However, the duration of contact is considered too small to lead to a significant leaching of amines from these products with sweat to the skin. It is therefore concluded that the use of household textiles and towels does not lead to significant exposure to 2,4-toluenediamine and benzidine and, consequently, does not lead to a significant cancer risk.

In carpets the amount of benzidine was found to range from 30 to 1100 ppm. Prolonged exposure to benzidine from carpets may occur by inhalation of air containing wastage of this product. In order to estimate this exposure the general characteristics of the wastage of carpets, and the accumulation of carpet dust in rooms needs to be known. As no information is available on this issue this route of exposure cannot be quantitated.

In summary, only in the case of bedclothes, watchstraps and ink does Mensink *et al.* (1997) provide sufficient information to perform a cancer risk assessment.

In the Netherlands products are regularly monitored by the Regional Inspectorate for Health Protection on the occurrence of carcinogenic amines. Recent data from this monitoring campaign revealed azo dyes to occur in tattoo bands, folders of paper, and textile toys (Vliet, 1998; Laurensse and Abdulovski, 1998; IWV, 1999). These products were therefore added to the above-mentioned database.

2.2 Uptake assessment

The exposure to carcinogenic aromatic amines from consumer products has two components. First amines may enter the body after being split off from azo dyes. This conversion may be performed by bacteria present on the skin or in the gastro-intestinal tract or by mammalian enzymes in the skin. Furthermore, consumer products may contain the amines in their so-called "free", i.e. unbound, form. Such "free" amines also may enter the body.

Basically the calculation of the daily, life-long, uptake rate of aromatic amines from consumer products consists of the estimation of the amount of the amine which is taken up in the period between the purchase and the disposal of the product (equal to one product cycle), i.e. $E_{eff,total\ amine}$, and the total number of product cycli during life. A detailed description of the calculation of $E_{eff,total\ amine}$ and its corresponding daily, life-long uptake rate is presented in Appendix 1. Table 1 summarizes the outcome of this calculation.

Table 1. Estimated daily, life-long, uptake rate of carcinogenic, aromatic amines from tattoo bands, folders of paper, bedclothes, textile toys, watch straps and ink ("free" amines included)

Product/ Material/ Route of exposure	*Amine*[1]	$E_{eff,total\ amine}$[2] *(µg)*	*No. of life-time product cycli*	*Life-long amine uptake (ng/day)*
Tattoo bands/ Nylon/dermal	Benzidine	9.1	1	0.4
Folders of paper Unknown/dermal	*o*-Anisidine	3.5	48-208	7.0-28
Textile toys Unknown/oral	2,4-Toluenediamine	510-2039	1	20-80
Bed clothes Unknown/dermal	4,4'-Diaminodifenylmethane	9.7-970	70	27-2700
Ink ("airbrush") Inhalatory + dermal	3,3'-Dichlorobenzidine *o*-Toluidine	23.8 12.0	10 10	9.3 4.7
Watch straps Leather/dermal	Benzidine	50-160	23.3	46-146

[1] Detected amine; [2] Amount of amine which, during a product cycle, is taken up via the skin or via the lungs.

3. Effect assessment

3.1 Hazard identification

Epidemiological studies have provided evidence for at least some azo-dye derived aromatic amines as being human carcinogens: benzidine and 2-naphthylamine were shown to induce urinary bladder cancer in workers in the azo-dye industry (see IARC, 1974; 1982; 1987, and references cited therein). Additionally, most aromatic amines tested in experimental animals also appear to be carcinogens. Target-sites for carcinogenesis in animals depend on the route of administration of the amine, and include liver, urinary bladder, hemopoietic organs, mammary gland, zymbal gland, and gastro-intestinal tract (Gold and Zeiger, 1997). Although many aromatic amines are expected to share a common pattern of bioactivation (oxidation and acetylation of the critical amine group, Chou *et al.*, 1995) and have, in part, target-sites in common, no clear relationship can be established between the structural features of an amine and its target organs.

3.2 Dose-response assessment

From the preceding chapter on exposure it is clear that, for the purpose of this report, the dose-response analysis can be restricted to benzidine, *o*-anisidine, 2,4-toluenediamine, 4,4'-diaminodifenylmethane, 3,3'-dichlorobenzidine and *o*-toluidine. All these amines were shown to be carcinogenic in experimental animals (Gold and Zeiger, 1997).

3.2.1 Benzidine

Although benzidine has proven carcinogenic activity towards humans an acceptable cancer risk level for this amine has not been established in the Netherlands, neither for the general population nor for workers.

An acceptable benzidine cancer risk level has been established by the U.S. EPA in 1993 (U.S. EPA, 1997). This risk level has also been used by others in their assessment of cancer risks associated with the use of textiles and leather goods colored with azo dyes, e.g. LGC (LGC, 1998). In their assessment U.S. EPA has estimated benzidine exposure in one of the industrial cohort studies described by Zavon *et al.* (1973). In this assessment two types of observations were combined: the benzidine levels in urine of exposed workers in this cohort and the relationship between oral benzidine exposure and urinary excretion determined in rhesus monkeys (Rinde and Troll, 1975). Based upon these data and using a one-hit extrapolation model, an oral slope factor of 230 per mg benzidine per kg body weight per day was calculated (U.S. EPA, 1993). From this a life-time daily exposure corresponding to one extra case of cancer per million persons exposed lifetime, i.e. a "Negligible Risk Level" (NRL) of 0.3 ng benzidine per person per day was calculated (IRIS, 1993; see also Zeilmaker *et al.*, 1999). A comparable estimate of 0.48 ng a day is obtained when the data used by U.S. EPA are combined with methodology adopted in the Netherlands (HCN, 1994; see also Zeilmaker *et al.*, 1999).

When the NRL of benzidine is calculated on the basis of the extrapolation of benzidine carcinogenicity from animals to man, a value considerably higher than 0.3 ng/day is extrapolated. For example when, as shown in Appendix 2, the chronic dose rate required to halve the probability of an experimental animal of remaining tumor free by the end of its standard life-span (TD_{50}, Gold and Zeiger, 1997) is taken as the starting point for the calculation of the NRL of benzidine a value of 238 ng/day is found. This value is almost 800 fold higher than calculated on the basis of the epidemiological data used by U.S. EPA.

As dose-response analysis should preferentially be based on observations in humans instead of on animal data a NRL of 0.3 ng/day was further used in calculating benzidine related cancer risks.

3.2.2 Other aromatic amines

In contrast with benzidine, carcinogenicity data in humans are not available for the amines *o*-anisidine, 2,4-toluenediamine, 4,4'-diaminodifenylmethane, 3,3'-dichlorobenzidine and *o*-toluidine. In the absence of suitable human carcinogenicity data NRL's traditionally are obtained by extrapolating carcinogenicity data from animals to man. Usually such an extrapolation rests on the assumption that the dose-response characteristics of chemical carcinogenicity are the same in animals and man. As shown above, when applied on benzidine, such an extrapolation would result in a NRL which is much higher than a NRL derived on the basis of epidemiological data on benzidine carcinogenicity. This finding indicates that the dose-response characteristics of benzidine carcinogenicity may be quite different in animals and man, with man possibly being the more sensitive species. Lacking conclusive evidence it was assumed that humans are sensitive to benzidine-related amines to a similar degree as may be interpreted from benzidine data.
For this reason the NRL's of benzidine related amines were not calculated in the traditional way, i.e. by direct extrapolation of carcinogenicity from animals to man. Instead, these NRL's were calculated by multiplying the NRL of benzidine (see above) by a factor, which corrects for differences in carcinogenic potency between a particular amine and benzidine. Provisional estimates of such correction factors were obtained from differences in TD_{50} values as reported for benzidine and related amines in animals (Gold and Zeiger, 1997, see also Zeilmaker *et al.*, 1999). For benzidine and 2,4-toluenediamine TD_{50}'s of 1.7 mg/kg/day and 2 to 4 mg/kg/day were reported. No TD_{50} is available for 4,4'-diaminodifenylmethane. However, the TD_{50} of a structural analogue (3,3'-dimethyl-4, 4'-diaminodifenylmethane) is available: 7 mg/kg/day. The TD50's of *o*-anisidine, 3,3'-dichlorobenzidine and *o*-toluidine were reported to be 30, 28 and 44 mg/kg/day. These TD50's were used to classify the carcinogenicity potency of their corresponding amines. Amines with a TD_{50} in animals which differs less than ten-fold from the TD_{50} of benzidine (2,4-toluenediamine; 4,4'-diaminodifenylmethane) are assumed equipotent carcinogens with respect to benzidine in

man[3]. Consequently, the NRL's of these amines were set equal to the NRL of benzidine, i.e. 0.3 ng/day (correction factor: 1). Similarly, amines with a TD_{50} in animals which differs more than ten-fold, but less than hundred-fold, from the TD_{50} of benzidine (*o*-anisidine, 3,3'-dichlorobenzidine and *o*-toluidine) are assumed to be one order of magnitude, i.e. tenfold, less potent human carcinogens than benzidine. Consequently, the NRL's of these amines were set equal to ten times the NRL of benzidine, i.e. 3 ng/day (correction factor: 10).

For comparative reasons NRLs were also calculated in the traditional way, i.e. on the basis of animal, instead of epidemiological, data (see Appendix 2). When the TD50's for amines as observed in rodents (Gold and Zeiger, 1997) are taken as a point of departure for the calculation of animal based NRLs, we would arrive at the following acceptable daily exposures leading to a 10^{-6} cancer risk levels for humans: 4200 ng per person for *o*-anisidine, 280-560 ng per person for 2,4-toluenediamine, 980 ng per person for 4,4'-diaminodifenylmethane, 3920 ng per person for 3,3'-dichlorobenzidine and 6160 ng per person for *o*-toluidine (see also Appendix 2). These NRLs are several orders of magnitude higher than NRLs derived on the basis of epidemiological data.

[3] Note that as benzidine shows, of all amines tested, the highest carcinogenic potency in animals this assumption reflects a "worse case" approach of the estimation of the carcinogenic potency of amines other than benzidine in humans, i.e. it estimates the lowest, most likely, value of the NRL.

4. Cancer risk assessment

4.1 Acceptable exposure limits for carcinogenic aromatic amines

For carcinogens without a threshold a $1 \cdot 10^{-6}$ lifetime risk level, i.e. one extra case of cancer per million persons exposed lifetime, is considered to be the "Negligible Risk Level" (NRL; Dutch equivalent: Verwaarloosbaar Risico, VR). A risk level that is 100 times higher ($1 \cdot 10^{-4}$ lifetime, i.e. one extra case of cancer per 10.000 persons exposed during life- time) is considered to be the "Maximum Permissible Risk Level" (MPRL; Dutch equivalent: Maximaal Toelaatbaar Risico, MTR).

4.2 Calculation of cancer risk

Given the daily, lifetime uptake rate of a carcinogenic amine and its NRL the 10^{-6} cancer risk is calculated as the ratio of these two numbers.

4.3 Cancer risk

In calculating cancer risks two approaches were followed. In the first approach the NRL/MPRL of benzidine was calculated from epidemiological data. NRLs/MPRLs of benzidine-related amines were obtained by correcting the NRL/MPRL of benzidine for differences in carcinogenic potency between a particular amine and benzidine. In the second, traditional, approach the NRL/MPRL of benzidine still was calculated from epidemiological data, but the NRLs/MPRLs of benzidine related amines were obtained from animal data. As shown in table 2 both approaches lead to quite different cancer risks. Taking the first approach all cancer risks were equal or in excess of the acceptable 10^{-6} risk level. In three cases even the 10^{-4} risk level was exceeded. In contrast, in the traditional approach, for only two products (bedclothes, watch straps) the cancer risk exceeds the acceptable 10^{-6} risk level.

Table 2. *Cancer risk of the exposure to aromatic amines from tattoo bands, folders of paper, bed clothes, textile toys, watch straps and ink ("free" amines included) using two different approaches.*

Product/ Material/ Route of exposure	*Amine**	*Life-long amine uptake (ng/day)*	*Cancer risk (first approach)*	*Cancer risk (traditional approach)*
Tattoo bands/ Nylon/dermal	Benzidine	0.4	1×10^{-6}	1×10^{-6}
Folders of paper Unknown/dermal	*o*-Anisidine	7.0-28	$2\text{-}9 \times 10^{-6}$	$1.7\text{-}6.7 \times 10^{-9}$
Textile toys Unknown/oral	2,4-Toluenediamine	20-80	$67\text{-}267 \times 10^{-6}$	$3.6 \times 10^{-8}\text{-}0.3 \times 10^{-6}$
Bed clothes Unknown/dermal	4,4'-Diaminodifenylmethane	27-2700	$90\text{-}9000 \times 10^{-6}$	$2.8 \times 10^{-8}\text{-}2.8 \times 10^{-6}$
Ink Inhalatory + Dermal	3,3'-Dichlorobenzidine *o*-Toluidine	9.3 4.7	3×10^{-6} 2×10^{-6}	2.4×10^{-9} 7.6×10^{-10}
Watch straps Leather/dermal	Benzidine	46-146	$153\text{-}487 \times 10^{-6}$	$153\text{-}487 \times 10^{-6}$

* Detected amine

5. Discussion

In order to calculate the cancer risks in Table 2 several assumptions had to be made. A proper interpretation of these risks needs a systematic evaluation of the assumptions made. This evaluation is presented below.

Life-long exposure

For bedclothes the calculation of the cancer risks assumes that life-long exposure occurs to this product. Whether or not this actually is the case needs specialized information on the long-term characteristics of consumer behavior, i.e. the frequency with which consumers buy and come into contact with products. Such information is not (yet) available. Consequently, it cannot be evaluated whether the assumed life-long exposure to bedclothes represents a "realistic case" (real exposure nearly life time) or a "worst case" (real exposure far less than lifetime) approach.

Similarly, for watch straps and folders of paper prolonged, but less than life-long, exposure was assumed. For tattoo bands, textile toys and ink the exposure to azo dyes from these products were even assumed to be far less than life-long. In order to calculate the life-time cancer risk the exposure to these products had to be corrected for its "less than life-long" character. This correction was performed by assuming that cancer risk is proportional to the cumulative exposure during the period in which the products is used.

Migration of azo dyes from the products

In the case of tattoo bands, textile toys and watchstraps it was assumed that all amines in these products migrate from the product to the skin or into the gastro-intestinal tract. In the case of tattoo bands this assumption is based on the experimental observation that such bands may completely loose their color when extracted with an aqueous solution. Similarly, experimental observations indicate that the sustained leaching with sweat or saliva may lead to the complete removal of amines from leather and textile (Zeilmaker *et al.*, 1999).

For textile toys and watchstraps, in contrast to tattoo bands, no experimental data are available for the migration of amines from folders of paper. So, in assessing the migration of amines from this product a "worst case" approach had to be taken, i.e. it was assumed that all of the amine present in the product leaches onto the skin.

The exposure to 4,4'-diaminodifenylmethane from bed clothes was assumed to be equal to ten times the amount of amine which leaches with sweat from the newly bought, unwashed, product. This assumption was directly extrapolated from the leaching of carcinogenic amines with sweat from garment (Zeilmaker *et al.*, 1999).

Extraction with sweat simulant as model for leaching with sweat

The uptake assessment of textile toys, bedclothes and watchstraps is based on the experimentally observed leaching of aromatic amines from textile and leather products with a sweat simulant. This leaching was assumed to represent the leaching of amines with sweat. Experimentally the leaching with the sweat simulant was determined by exposing 1 gram of the product for 16 hrs., at 37 °C, to 100 ml of the simulant. Although these conditions guarantee an optimal extraction of the amine from the product they differ from the conditions which prevail on the skin when leaching with sweat takes place. On the skin the amount of sweat is much smaller than the amount of the material which is being leached, whereas under the aforementioned experimental conditions just the opposite situation occurs. Furthermore, sweat evaporates on the skin. This process will decrease the efficiency of leaching, especially at relative long exposure times. Finally, the used extraction time of 16 hrs. will, even under extreme conditions such as athletic endurance, not occur.

In conclusion, it is expected that the experimentally determined extraction with a sweat simulant overestimates the leaching with sweat.

Probability of azo dyes and aromatic amines appearing in products

The probability of azo dyes and aromatic amines appearing in consumer products is based on the frequency with which these compounds were found during sampling of lots of these products. In interpreting the accuracy of this probability it should be kept in mind that during sampling a positive selection for products which contain azo dyes and amines inevitable has taken place. So, the true probability of azo dyes and amines appearing in products, which are available on the market, may be substantially lower than used in the calculations in this report.
In this context it is worth mentioning that a recent survey on the occurrence of carcinogenic azo dyes in garment revealed these compounds to be present in only 1 piece of textile garment (textile jacket)(Consumentengids, 1999)

Dose-response assessment

In the present risk assessment the NRL of benzidine is taken as the reference point for the calculation of amine specific cancer risks. This risk level, i.e. 0.3 ng/day, is obtained by extrapolating the occurrence of urinary bladder cancer as observed in workers exposed to benzidine to the general population.

The method, which was used to derive the limit value of benzidine, has several uncertainties. Firstly, there are some questions about the accuracy of the exposure and effect assessment of benzidine in the epidemiological data used to derive the NRL, i.e. the study of Zavon *et al.* (1973). In this study the exposure to benzidine was quantified by measuring benzidine in urine of exposed workers by means of the chloramine-T reagent. Furthermore, the observed bladder carcinogenicity was attributed to benzidine exposure only. It is unclear how specific the chloramine-T reagent assay is towards benzidine and whether concomitant

exposure to other aromatic amines might have confounded benzidine exposure-response relationships. When in the Zavon study the exposure estimate of benzidine has been biased by other amines (and possible other, unknown compounds) this may have led to an overestimation of the true benzidine exposure. Consequently, the steepness of the dose-response relationship between (the true) benzidine exposure and the observed carcinogenicity would have been underestimated. On the other hand, when the observed carcinogenicity was not solely caused by exposure to benzidine, attributing this carcinogenicity to benzidine only may have led to an overestimation of the carcinogenic potency of benzidine. To resolve these issues is beyond the scope of this report. Here, we suffice with stating that in the Netherlands both issues are currently being reviewed in a joint effort of scientist of the National Institute of Public Health and the Environment and the Dutch Expert Committee on Occupational Standards of the Health Council of the Netherlands. This review focuses on the validity of the Zavon study as a basis for the derivation of the NRL of benzidine, the evaluation of more recently published epidemiological data on benzidine carcinogenicity and the use of animal data as the starting point for the scaling of the carcinogenic potency of aromatic amines in humans. In this context also the remark made by IARC on this specific cohort study should be noticed. In their Monograph series (IARC, 1982) IARC states: "Of the epidemiological studies available to the Working Group, only that of Zavon *et al.* (1973) provides sufficient information on levels of exposure to benzidine to serve as a basis for quantitative risk assessment. This study allows very crude estimates of the carcinogenic potency of benzidine to be made."

Finally, the concept used by U.S. EPA in their hazard characterization approach, i.e. urinary benzidine levels are taken as a valid surrogate for the effects observed, irrespective of the route of exposure. Clearly, benzidine levels in urine may well represent the exposure to benzidine of the urinary bladder epithelium, the target tissue for carcinogenesis. However, there is clear evidence that benzidine-metabolites are the ultimate carcinogenic species, and that these are thought to be generated outside the bladder epithelium, i.e. mainly in the liver (Chou *et al.*, 1995). Thus, it can be anticipated that different exposure routes may result in quite different amounts of critical metabolites in the urinary bladder lumen, implying in parallel quite different cancer responses as well. Clearly, the last two points of uncertainty may have substantial influence on the acceptable cancer risk level derived at.

Consumer specific risk assessment v.s. product specific risk assessment

The calculation of the cancer risks presented in this report incorporates the probability (P) that consumers, in using a particular product, face exposure to a carcinogenic azo dye and its constituting "free" amine. In this calculation a probability much smaller than 1 corresponds with the situation in which only a small fraction of the products available on the market contains a carcinogenic amine. Consequently, the probability that consumers, who "randomly" buy the product, face exposure to these compounds is low. On the other hand a probability close to 1 corresponds to a situation in which consumers, unwillingly, have a preference for buying products which contain carcinogenic amines. The cancer risks

associated with the latter situation can easily be obtained by attributing *P* a value of 1, instead of its observed value, in calculating the amine uptake from products (see Table 3).

Table 3. *Consumer vs. product specific cancer risk of the exposure to aromatic amines from tattoo bands, folders of paper, bed clothes, textile toys, watch straps and ink ("free" amines included) using the first approach (see Table 2).*

Product/ Material/ Route of exposure	*Amine**	*Cancer risk (consumer specific)*	*Cancer risk (product specific)*
Tattoo bands/ Nylon/dermal	Benzidine	1×10^{-6}	1×10^{-6}
Folders of paper Unknown/dermal	*o*-Anisidine	$2\text{-}9 \times 10^{-6}$	$12\text{-}53 \times 10^{-6}$
Textile toys Unknown/oral	2,4-Toluenediamine	$67\text{-}267 \times 10^{-6}$	$94\text{-}376 \times 10^{-6}$
Bed clothes Unknown/dermal	4,4'-Diaminodifenylmethane	$90\text{-}9000 \times 10^{-6}$	$900\text{-}90000 \times 10^{-6}$
Ink Inhalatory + Dermal	3,3'-Dichlorobenzidine *o*-Toluidine	3×10^{-6} 2×10^{-6}	5×10^{-6} 3×10^{-6}
Watch straps Leather/dermal	Benzidine	$153\text{-}487 \times 10^{-6}$	$1131\text{-}3846 \times 10^{-6}$

* Detected amine; Example of the calculation of the product specific risk: Folders of paper, consumer specific risk $2\text{-}9 \times 10^{-6}$ (see Table 2) with P = 0.17 (see Appendix 1), so the product specific risk becomes 2/0.17 – 9/0.17 = $12\text{-}53 \times 10^{-6}$.

Cancer risk assessment of azo dyes and aromatic amines in consumer products: Concluding remarks

In a previous RIVM report a cancer risk assessment was performed for garment and footwear in which azo dyes containing benzidine, *o*-tolidine, *o*-dianisidine and 2,4-toluenediamine were found (Zeilmaker *et al.*, 1999). In the present report this risk assessment was extended to benzidine, *o*-anisidine, 2,4-toluenediamine, 4,4'-diaminodifenylmethane, 3,3'-dichlorobenzidine and *o*-toluidine occurring in products like tattoo bands, folders of paper, textile toys, bed clothes, watch straps and ink. Without exception the risk assessment showed that the amounts of amines present in these products pose an unacceptable cancer risk to consumers using these products.

Alternatively one might ask what amounts of amines in the mentioned products would lead to an acceptable exposure, i.e. a daily, life-long uptake rate which is just equal to the NRL based on the precautionary approach. For the products investigated the latter amounts are shown in Table 4. This table shows that the amounts of amines in the products investigated which would lead to an acceptable cancer risk are well below 30 ppm, i.e. the value used by the EU (and the Dutch authorities) as an acceptable limit for aromatic amines in a number of consumer products. Furthermore Table 4 illustrates that, even when present in minute quantities, the presence of carcinogenic amines in products may pose an unacceptable cancer risk to consumers. In fact, from this approach it can be concluded that the only effective way of avoiding this risk consists of a severe reduction of the levels of carcinogenic amines in consumer products. Again, as stated before, when the more traditional risk assessment approach is taken (NRLs/MPRLs of benzidine-related amines based on animal toxicity data) this picture changes substantially.

Table 4. *Product specific risk assessment: Amounts of carcinogenic, aromatic amines in consumer products which lead to a daily, life-long, uptake rate at the level of the NRL using the first approach (see Table 2).*

Type of product	*Amine*	*Actual amount (μg/g)*[1]	*Acceptable amount (μg/g)*[2]
Garment			
Underwear	Benzidine	1368	4
Blouse	o-Tolidine	2796	0.6
Children's legging	Benzidine	1112	0.5
Children's sweater	o-Dianisidine	337	5
Underwear	Benzidine	950	0.3
Children's coat	o-Dianisidine	119	3
	o-Tolidine	35	3
	Benzidine	17	0.3
Footwear			
Children's slipper	Benzidine	381	4
Children's slipper	2,4-Toluenediamine	210	21
Shoe	Benzidine	161	0.4
Sportsshoe	o-Dianisidine	589	4
Other products			
Tattoo bands	Benzidine	113	113
Folders of paper	o-Anisidine	257	5-21
Toys	2,4-Toluenedamine	359	1-4
Bed clothes	4,4'-Diaminodifenylmethane	1020	0.01-1
Watch straps	Benzidine	1230	0.3-1
Ink	3,3'-Dichlorobenzidine	340	69
	o-Toluidine	170	65

[1]Amount found in the product; [2] Amount in the product, which would lead to a daily, life-long, uptake rate equal to the NRL. Example of the calculation of the acceptable amount: underwear containing 1368 ppm benzidine corresponding, at $P = 0.08$, with a consumer specific risk of 25×10^{-6} (Zeilmaker *et al.*, 1999). The product specific risk associated with such underwear then is $25/0.08 = 312 \times 10^{-6}$. The amount of benzidine in underwear corresponding with a 1×10^{-6} risk then is 1368/312 = 4.4, rounded 4, ppm.

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Appendix 1 Exposure Assessment

This appendix describes the calculation of the exposure of consumers to carcinogenic aromatic amines from tattoo bands, folders of paper, textile toys, bed clothes and leather watch straps.

Uptake assessment

The oral/dermal exposure of carcinogenic, aromatic, amines from consumer products has two components.

Firstly, azo dyes may migrate from a product onto the skin. Once on the skin the azo dye may be absorbed or, in the case of oral exposure, be swallowed. In the skin part of the absorbed azo dye can be split into its constituting amine. The amine may then migrate to the blood. Splitting of the dye may also occur in the liver and in the gastro-intestinal tract. In the latter case the released amine may enter the body by absorption across the gastro-intestinal wall. Secondly the amine itself ("free" amine) may migrate from the product onto the skin. As with amine which is released from an azo dye in the skin or the gastro-intestinal tract the migrated "free" amine may be taken up by absorption through the skin or by absorption across the wall of the gastro-intestinal tract.

The principle of the assessment of the dermal/oral exposure of amines from consumer products is shown in Fig. 1. Exposure assessment starts with an estimation of the probability that a product contains carcinogenic azo dyes and "free" amines. For such a product the migration of "free" amine azo dye is estimated. Next the fraction of the product which comes into contact with the skin (skin contact factor) is taken into account. Applying these factors on the migrated amounts of azo dye and "free" amine results in the calculation of the amounts of azo dye ($A^*_{derm,dye}$, g) and "free" amine ($A^*_{dermal,\ "free"\ amine}$, g) which may reach the skin. After correction for the absorption of the azo dye and the conversion of the absorbed dye into its constituting amine the total uptake of the amine ($E_{eff,total\ amine}$, g) is calculated as the sum of the absorbed amounts of "free" amine and amine which is released from the azo dye.

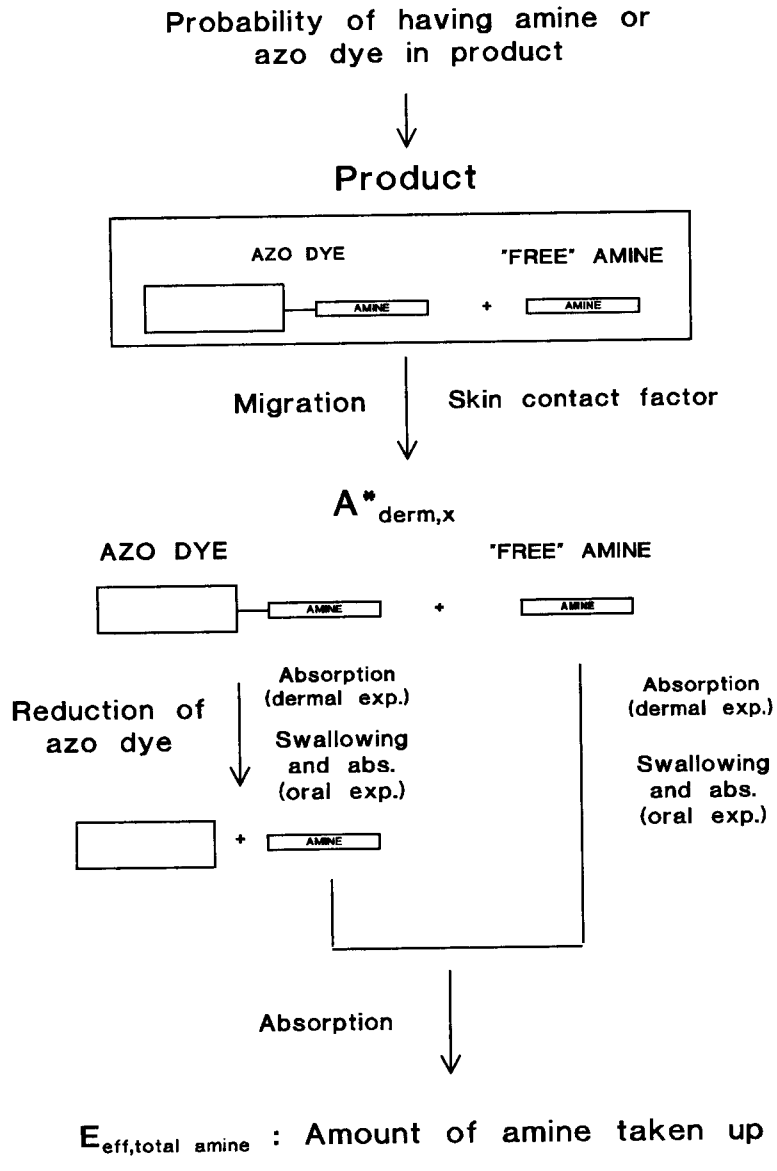

Fig. 1 Scheme for the estimation of the oral/dermal uptake of carcinogenic amines from consumer products containing azo dyes and "free" amines. x: azo dye or "free" amine.

The uptake of carcinogenic aromatic amines from products during the period between the purchase and the disposal of the product, the uptake $E_{eff,total\ amine}$ during one product cycle, is calculated as the product of the probability that a product contains a "free" amine and its corresponding amine containing azo dye, the migration of the "free" amines and the azo dye from the product onto the skin and the absorption of the migrated "free" amine and azo dye in the body:

$$E_{eff,total\ amine} = P \cdot F_{skin} \cdot W \cdot \left[F_{migr,azo} \cdot c_{azo} \cdot F_{abs,azo} + F_{migr,free} \cdot c_{free} \cdot F_{abs,free}\right]$$

with:

$E_{eff,total\ amine}$	Expected uptake of amine during one product cycle (g)
P	Probability that a product contains a carcinogenic azo dye and its corresponding "free" amine (no dimension)
F_{skin}	Skin contact factor (no dimension)
W	Product weight (g)
$F_{migr,azo}$	Fraction of the amine which, as part of an azo-dye, migrates from the product (no dimension)
c_{azo}	The concentration of amine as part of an azo-dye (g amine/g product)
$F_{abs,azo}$	Fraction absorbed of amine which has migrated as part of an azo-dye (no dimension)
$F_{migr,free}$	Fraction of the "free" amine which migrates from the product (no dimension)
c_{free}	The concentration of "free" amine (g amine/g product)
$F_{abs,free}$	Fraction absorbed of migrated "free" amine (no dimension)

In the case of garment and footwear all of the parameters necessary to calculate $E_{eff,total\ amine}$ could be estimated either from literature sources or by means of experimental research (Zeilmaker *et al.*, 1999). Unfortunately for the products evaluated in this report less information is available. For, for these products only the total amount of amine in the products, i.e. the sum of c_{azo} and c_{free} is known. However, as has been shown for garment and footwear, the contribution of the "free" amine (c_{free}) to $E_{eff,total\ amine}$ is negligibly low. When the contribution of c_{free} to $E_{eff,total\ amine}$ is neglected the latter becomes:

$$E_{eff,total\ amine} \approx P \cdot F_{skin} \cdot W \cdot F_{migr,azo} \cdot c_{azo} \cdot F_{abs,azo}$$

The (mean) uptake rate of the amine during one product cycle is obtained by dividing $E_{eff,total\ amine}$ by the duration of that cycle (days). In some cases this uptake rate is equal to the life-time, daily, uptake rate. For example, when a product is bought yearly (product cycle: 1 year) during the entire life-time of 70 years (number of life-time product cycli: 70), the life-time uptake rate is equal to $70 \cdot E_{eff,total\ amine}/70$ years = $E_{eff,total\ amine}$ per year[4].

[4] In general, when a product is bought at a frequency of once in, say, α years and the number of life-time product cycli is, say, β, the total uptake is $\beta \cdot E_{eff,total\ amine}$ and the life-time yearly uptake rate is equal to $\beta \cdot E_{eff,total\ amine}/70$, which differs from the uptake rate during a

As examples of the calculation of $E_{eff,total\ amine}$ the daily, life-long uptake rate of benzidine from underwear and the uptake of *o*-dianisidine from a string of a children's sweater are presented here.

Underwear

In between wearing, underwear is often washed. In this way quite some amines are removed from the product, leaving a relative small fraction of amines remaining for leaching with sweat during wearing (Zeilmaker *et al.*, 1999). For this situation it was estimated that the total amount of amines which, during the use of the product, may leach from each gram of textile with sweat is equal to ten times the amount which leaches from the new, unwashed, product.

Probability of a benzidine containing azo dye appearing in underwear	0.08
Amount of benzidine, as part of an azo-dye, in the product (new, unwashed product)	1368 µg/g
Fraction of benzidine migrated	0.0046
Product weight	18 grams
Skin contact factor	1
Calculated migration: 0,08 · 1368· 0,0046 · 18 · 1 = 9,1 µg	
Fraction absorbed	0.1
Calculated uptake: 9,1 · 0.1 · 1000 = 910 ng	

Assuming underwear to be bought yearly (product cycle: 1 year) during the entire life-time (no. of life-time product cycli: 70) the calculated uptake corresponds with a life-time, daily, uptake of 910 ng · 70/(70 years · 365 days per year) = 2.5 ng benzidine per day.

String of a children's sweater

Probability of an *o*-dianisidine containing azo dye appearing in a sweater	0.08
Amount of *o*-dianisidine, as part of an azo-dye, in the product (new, unwashed product)	337 µg/g
Fraction of *o*-dianisidine migrated	0.015
Product weight	3 grams
Skin contact factor	1
Calculated migration: 0,08 · 337· 0,015 · 3 · 1 = 1.2 µg	
Fraction absorbed	1
Calculated uptake: 1,2 · 1 · 1000 = 1200 ng	

product cycle, i.e. $E_{eff,total\ amine}/\alpha$ per year (note that both uptake rates differ by a factor $\alpha \cdot \beta/70$; furthermore the product $\alpha\beta$ is lower or equal to the duration of life-time).

Assuming this product to be bought yearly (product cycle: 1 year) for a period of up to 15 years (no. of life-time product cycli: 15) this uptake corresponds with a daily, life-time, uptake rate of 1200 ng · 15/(70 years · 365 days per year) = 0.7 ng *o*-anisidine per day.

Specific products

Tattoo bands

Tattoo bands are ornaments which are worne by children in the neck, on the arm or on the ankles. The bands consist of darkly stained nylon.

Analysed materials

Recently the Regional Inspectorate for Health Protection investigated a number of tattoo bands on the occurrence of carcinogenic azo dyes. Of 10 investigated bands 8 contained the amine benzidine (IVW, 1999). The probability that tattoo bands contain a benzidine containing azo dye therefore is estimated to be 0.8.
The amount of benzidine found in tattoo bands ranged from 11 to113 ppm (mg/kg).

Uptake assessment and parameter values

When wearing tattoo bands azo dyes may migrate from the product onto the skin by leaching with sweat. In order to assess this exposure the amount of azo dye which, during wearing, leaches from the product with sweat must be known. Such information is not available. The above mentioned amounts of benzidine are determined by extraction with citrate buffer (pH = 6, 30 min, 60 °C). As shown in Zeilmaker *et al.* (1999) such an extraction may grossly overestimate the leaching of azo dyes from products with sweat.

However, during the extraction of the bands with citrate buffer it was observed that, in a number of cases, a total removal of the azo dye from the product occurred (Van Hemert, personal communication). This indicates that tattoo bands are available on the Dutch market from which azo dyes can fully be removed by extraction with an aquaous solution. Though it has to be shown that such removal may also occur by leaching on the skin with sweat, it is assumed that azo dyes leach completely from tattoo bands with sweat onto the skin.

It is assumed that children (maximally) may wear three tattoo bands at the same time (one in the neck, one on the arm and one on the ankle, total weight (W) around 1 gram, this weight coming into contact with the skin, F_{skin} equal to 1) and that exposure is limited to one set of tattoo bands, i.e. it is assumed that tattoo bands are bought only once in a life-time (β equal to 1, for tattoo bands, being a trendy product, a product cycle of 0.5 years is assumed). All of the azo dyes in the band is assumed to leach from this product ($F_{migr,azo}$ equal to 1). Of the leached dye only 10 % is expected to enter the body ($F_{abs,azo}$ equal to 0.1, Zeilmaker *et al.*, 1999). The probability P of the occurrence of benzidine in tattoo bands is set at 0.8.

Effect Assessment

The NRL of benzidine is set at 0.3 ng/day (Zeilmaker *et al.*, 1999).

Folders of paper

Folders of paper are used by children in making all kinds of paper ornaments. Examples are paper aeroplanes, animal figures made of paper and collages of paperwork glued together.

Analysed material

Recently the Regional Inspectorate for Health Protection investigated a number of folders on the occurrence of carcinogenic azo dyes. Of 6 investigated bands 1 contained the amine *o*-anisidine (Laurensse, 1998a). The probability that folders contain an *o*-anisidine containing azo dye therefore is estimated to be 0.17. The amount of *o*-anisidine found in the paper was 257 ppm (mg/kg).

Uptake assessment and parameter values

Dermal exposure to azo dyes from folders of paper may take place when children use such folders in combination with paint or glue. The latter media may moisten the hands and, at the same time, the folders. In this way azo dyes dissolved in water and/or diluted glue may come into contact with the skin. In order to estimate such exposure the leaching of azo dyes with glue and/or water from folders of paper has to be known. Such information is available: the above mentioned amount of *o*-anisidine was determined by extraction of the folder with citrate buffer (pH = 6, 30 min, 60 °C).

The found *o*-anisidine is assumed to leach completely from the folders ($F_{migr,azo}$ equal to 1). Furthermore, the part of the product from which *o*-anisidine leaches comes directly into contact with the skin (F_{skin} equal to 1). The probability P of folders to contain an *o*-anisidine containing azo dye was set at 0.17. One folder of paper was assumed to measure 100 cm^2 and to weigh (W) 0.8 gram (a piece of A4 paper measures 625 cm^2 and weighs 5 grams). Only 10% of the amine present in the folders was assumed to be taken up in the body ($F_{abs,azo}$ equal to 0.1, Zeilmaker *et al.*, 1999). Folders of paper are assumed to be monthly (product cycle: 1 day; β equal to 48) or weekly (product cycle: 1 day; β equal to 208) used for a period of (maximally) 4 years.

Effect Assessment

The NRL of *o*-anisidine is set at 3 ng/day.

Textile toys

Teddy bears, puppets and clowns are examples of textile toys in which carcinogenic azo dyes are found.

Analysed material

Recently the Regional Inspectorate for Health Protection investigated a number of textile toys on the occurrence of carcinogenic azo dyes. Of 7 toys investigated 5 contained the amine 2,4-toluenediamine (Laurensse, 1998b). The probability that toys contain 2,4-toluenediamine therefore is estimated to be 0.71. The amount of 2,4-toluenediamine found ranged from 30 to 359 ppm (mg/kg).[5]

In two toys traces of the carcinogenic amines 2,4-diaminoanisole and *o*-toluidine were found. As no quantitative information is available on the amounts of 2,4-diaminoanisole and *o*-toluidine in textile toys the uptake of these amines could not be assessed.

Uptake assessment and parameter values

The exposure to 2,4-toluenediamine from textile toys occurs by sucking on these products. In order to assess the uptake of 2,4-toluenediamine via this route of exposure one has to know the leaching of the amine from textile with saliva. In a previous report the leaching of azo dyes from textiles with saliva was assumed to be equal to the leaching with sweat (Zeilmaker *et al.*, 1999). Though the latter form of leaching is rather inefficient, i.e. only a small fraction of the dye present in the product is removed each time it is used, the sustained use of textile ultimatally may lead to the complete total removal of the dyes from the product (Zeilmaker *et al.*, 1999). In the case of textile toys the assumption of sustained use and, consequently, a complete leaching of 2,4-toluenediamine from the product therefore seems reasonable ($F_{migr,azo}$ equal to 1).

First it is assumed that texile toys are bought once in a life-time (β equal to 1) and that they are daily used for a period of 6 to12 months (product cycle equal to 6 to 12 months). Then it is assumed that 20 cm^2 of the toys is regularly sucked on. Given textile weight to range from 1 to 4 gram per 10 cm^2 this corresponds with 2 (light textile) to 8 (heavy textile) grams of textile (W). This part of the product comes into direct contact with the skin (F_{skin} equal to 1). The oral route of exposure being the route of entry of the migrated dye a complete absorption of the amin herin is assumed ($F_{abs,azo}$ equal to 1, Zeilmaker *et al.*, 1999). The probability of 2,4-toluenediamine to occur in textile toys was set at 0.71.

Effect assessment

The NRL of 2,4-toluenediamine is set at 0.3 ng/day.

[5] Mensink *et al.* (1997) reports a range of 50 to 480 ppm for the amounts of 2,4-toluenediamine in textile toys.

Bed clothes

Analysed material

Mensink *et al.* (1997) reports amounts of 4,4'-diaminodifenylmethane in bed clothes to range from 40 to 1020 ppm (mg/kg). In this report a probability of 0.1 is mentioned for the occurrence of carcinogenic azo dyes in textile products.

Uptake assessment and parameter values

During sleeping exposure to 4,4'-diaminodifenylmethane may occur when this amine leaches from bed clothes with sweat. This exposure therefore can be compared with the leaching of amines from garment with sweat. The procedure for assessing the uptake of amines which results from such leaching is described in Zeilmaker *et al.* (1999). From this procedure it follows that, as a result of the removal of azo dyes from the product by washing, the total exposure to amines which are part of an azo dye from textile is at most ten times the amount of the amine which can be leached with sweat from newly bought, unwashed, textile. In garment a range of 0.0005 to 0.05 was found for the fraction of amine which leaches with sweat from the new, unwashed product (Zeilmaker *et al.*, 1999). So, the fraction migrated of the dye ($F_{migr,azo}$) ranges from 0.005 to 0.5. Furthermore, usually only a small fraction of the skin, i.e. the part which is not protected by pyamas, comes into direct contact with bed clothes. This fraction is arbitrarily set at 0.1. Consequently the fraction of the skin only indirectly comes into contact with bed clothes is 0.9. It is assumed that the exposure to azo dyes which results from the latter contact is one order of magnitude lower than that of direct contact (Zeilmaker *et al.*, 1999). The skin contact factor for the exposure to azo dyes from bed clothes therefore is $0{,}1 \cdot 1 + 0{,}9 \cdot 0{,}1 = 0.19$ (F_{skin} equal to 1).

Given an adult body surface of 2 m^2, half of this area to contact the skin, and a textile weight of 1 gram per 10 cm^2 (light textile) 1000 grams (W) of bed clothes may directly or indirectly come into contact with the skin. A probability of 0.1 was used for the occurrence of carcinogenic azo dyes in textile products. Only 10% of the migrated amine present in the azo was assumed to be taken up in the body ($F_{abs,azo}$ equal to,0.1). Bed clothes are thought to be bought once a year (product cycle: 1 year) during the entire life (β equal to 70).

Effect assessment

The NRL of 4,4'-diaminodifenylmethane is set at 0.3 ng/day.

Leather watch straps

Analysed material

Mensink *et al.* (1997) reports amounts of benzidine in leather watch straps to range from 70 to 1230 ppm (mg/kg). The probability of carcinogenic azo dyes appearing in watch straps is estimated at 0.12 (Mensink *et al.*, 1997).

Uptake assessment and parameter values

Sustained exposure to benzidine from leather watch straps occurs by leaching of this amine with sweat. Such exposure can be compared with the leaching of amines from leather footwear. As mentioned in Zeilmaker *et al.* (1999) the latter exposure may lead to the complete removal of amines from the product, i.e. $F_{migr,azo}$ is assumed to be equal to 1. Of the migrated amine only 10% is thought to be taken up in the body ($F_{abs,azo}$ equal to 0.1).

The product weight W is assumed to range from 3 to 10 grams. All of this product directly comes into contact with the skin (F_{skin} equal to 1). The probability for benzidine containing azo dyes to occur in watch straps is et at 0.13. Leather watch straps are assumed to be life-long bought every three years (product cycle: 3 years; β: 70/3).

Effect assessment

The NRL of benzidine is set at 0.3 ng/day.

Given the highest amounts of the amines found the calculations of the life-time, daily, amine uptake from tattoo bands, folders of paper, textile toys, bed clothes and watch straps are as shown in Table 5.

Table 5. Estimated uptake of carcinogenic, aromatic amines from tattoo bands, folders of paper, textile toys, bed clothes and watch straps ("free" amines included)

Product/ Material/ Route of exposure	*Amine*[1]	*Amount (μg/g)*[2]	*Fraction migrated*[3]	*Weight (g)*[4]	*Fraction absorbed*[5]	*Skin Contact Factor*[6]	*Probability of azo dye occurring*[7]	$E_{eff,total\ amine}$ *(μg)*	*Duration of product cycle (years)*[8]	*No. of life-time product cycli*[9]	*Life-long amine uptake (ng/dag)*
Tattoo bands/ nylon/dermal	Benzidine	113	1	1	0.1	1	0.80	9.1	½	1	0.35
Folder of paper/ unknown/dermal	*o*-Anisidine	257	1	0.8	0.1	1	0.17	3.5	1/365	48-208	7.0-28
Textile toys/ unknown/oral[¶]	2,4-Toluenediamine	359	1	2-8	1	1	0.71	510 - 2039	½ - 1	1	20-80
Bed clothes/ unknown/dermal	4,4'-Diaminodifenyl methane	1020	0.005-0.5	1000	0.1	0.19	0.10	9.7 - 970	1	70	27-2700
Watch straps/ leather/dermal	Benzidine	1230	1	3-10	0.1	1	0.13	50-160	3	70/3	46-146

[1] Detected amine; [2] Amount of amine detected in product, i.e. amine which is part of an azo dye (c_{azo}); [3] Fraction of the amine, as part of an azo dye, which migrates from the product ($F_{migr,azo}$); [4]Product weight (W); [5]Fraction absorbed of the migrated amine ($F_{abs,azo}$); [6] Fraction of the product which effectivily comes into contact with the skin (F_{skin}); [7] Probability that a product contains a carcinogenic azo dye; [8] α; [9] β.

Ink ("airbrush")

"Airbrush" is a painting technique in which ink is sprayed onto paper or metal by means of a spraying can or by mouth. Typical users of the "airbrush" technique are professionals like architects and maquette builders and children coloring paperwork.

Professional use of the "airbrush" technique ranges from spraying a few droplets of ink to spraying of several milliliters. Spraying is usually performed by means of an air pressure spraying can. When used protective measures are recommended.
Children may use the "airbrush" technique by blowing ink directly out of a pencil.

Analyzed material

Mensink *et al.* (1997) reports amounts of 3,3'-dichlorobenzidine in "airbrush" ink to range from 80 to 340 ppm (mg/kg). Similarly amounts of *o*-toluidine ranging from 60 to 170 ppm (mg/kg) were reported. The probability of occurrence of these amines to occur in ink is estimated at 0.63 (Mensink *et al.*, 1997).

Uptake assessment and parameter values

In assessing the exposure of consumers to carcinogenic aromatic amines from "airbrush" ink two scenarios were evaluated: children blowing ink directly out of a pencil onto paper and hobbyists mimicking professional use at home.

Regarding children blowing ink from a pencil onto paper it was found that, at least for pencils which are available on the Dutch market, a direct spill over of ink from the pencil onto the skin during normal spraying is negligibly low. We assume that children will only accidentally be exposed to ink, i.e. when ink is (un)intentionally sprayed direct on the skin instead of on paper. We assume that such an event occurs ten times during the period in which the product is used. For pencils available on the Dutch market, the (maximum) amount of ink which can be sprayed on the skin was found to be 10 · 1 mg = 10 milligrams of ink. Starting with a content of 340 ppm 3,3'-dichlorobenzidine in ink the total amount of 3,3'-dichlorobenzidine which is directly sprayed onto the skin is 10 · 340 = 3400 ng 3,3'-dichlorobenzidine. Of this amount only 10% is taken up (F_{abs} = 0.1; Zeilmaker *et al.*, 1999). Given a probability of 0.63 of 3,3'-dichlorobenzidine to occur in ink an uptake ($E_{eff,total\ amine}$) of 3400 ng · 0.1 · 0.63 = 214 ng is calculated. Assuming the product to be bought once in a life-time this uptake corresponds with a daily, life-time, uptake rate of 214 ng/(70 years · 365 days per year) = 0.008 ng/day. Similarly an uptake of 107 ng, resp. 0.004 ng/day, is calculated for ink containing 170 ppm *o*-toluidine.

Regarding hobbyists mimicking professional use at home the following exposure scenario was evaluated. The period in which a specific lot of ink is used, i.e. the product cycle, is assumed to be 1 year. In this period the product is assumed to be used 4 times per

month. During use it is assumed that 2.5 ml of ink is sprayed during a period of 60 minutes. So, during 1 year 48 · 2,5 ml = 120 ml of ink will be sprayed. Assuming a density of 1 g/cm^3, this volume weights 120 grams. Spraying is assumed to occur in a (passively) ventilated room (volume: 20 m^3; ventilation rate: 12 m^3/hr; height: 150 cm)(Bremmer and van Veen, 1999). After spraying has stopped an additional stay of 30 minutes in the room is assumed. Sprayed ink may be taken up by inhalation via aerosol droplets generated in the spraying or by deposition of part of the sprayed ink on the skin. The uptake which results from these routes of exposure was estimated with the sprayed-cloud model of the computer program CONSEXPO 3.0 (see Appendix 3 for specifications).

Exposure by inhalation of aerosol droplets

Based on their vapor pressure 3,3'-dichlorobenzidine and *o*-toluidine were classified as non-volatile chemicals. In accordance with the spraying of paint (Bremmer and van Veen, 1999) the spraying of ink is assumed to generate a sphere aerosol cloud of 1 m^3. This aerosol is assumed to contain droplets with a diameter of 50 µm. The aerosol is thought to contain 5% of the sprayed ink (Bremmer and van Veen, 1999). When inhaled droplets of 50 µm size deposit in the oral cavity (nose, mouth and throat), not in the trachea and deeper parts of the lungs (Freijer *et al.* 1997). After deposition the droplets are transported from the oral cavity into the gastro-intestinal tract by swallowing. For ink containing 340 ppm 3,3'-dichlorobenzidine a daily uptake rate of 0.68 ng 3,3'-dichlorobenzidine/kg/day is calculated (see Appendix 3). This uptake corresponds with an uptake during one product cycle of 0.63 · 0,68 ng/kg/day · 70 kg · 365 days/year = 10946 ng/year 3,3'-dichlorobenzidine is calculated for an adult weighing 70 kg. Given a sprayed amount of 120 ml · 340 µg/ml · 1000 ng/µg = 4,1 · 10^7 ng 3,3'-dichlorobenzidine the fraction of this compound which is taken up is 10946 ng/(4,1 · 10^7 ng) = 2.7 · 10^{-4}.

The total period in which the "airbrush" technique is used is estimated to be maximally 10 years. With this assumption the life-time, daily, inhalatory uptake rate of 3,3'-dichlorobenzidine becomes 10 years · 10946 ng/year /(70 years · 365 days/year) = 4.3 ng/day. Similarly for ink containing 170 ppm *o*-toluidine a life-time daily uptake rate of 2.2 ng/day is calculated.

Dermal exposure via spilled aerosol droplets

0.5 % of the sprayed droplets are assumed to be spoiled onto the skin (Bremmer and Van Veen, 1999). In this case a daily dermal uptake of 0.80 ng/kg/day is calculated (see Appendix 3). So, during a product cycle of 1 year an uptake of 0.63 · 0.80 ng/day · 70 · 365 days/year = 12877 ng 3,3'-dichlorobenzidine is calculated. Given an amount of 4,1 · 10^7 ng 3,3'-dichlorobenzidine sprayed the fraction of this compound in ink which is taken up dermally is 12877 ng/(4,1 · 10^7 ng) = 3.1 · 10^{-4}.

The life-time, daily, uptake rate of 3,3'-dichlorobenzidine then becomes 10 years · 12877 ng/(70 years · 365 days/year) = 5.0 ng/day. Similarly, for ink containing 170 ppm *o*-toluidine a life-time daily uptake rate of 2.5 ng/day is calculated.

A summary of the calculations of the life-time, daily, amine uptake from "airbrush" ink resulting from the hobbyist's scenario is presented in Table 6.

Effect assessment

The NRL of 3,3'-dichlorobenzidine and *o*-toluidine were set at 3 ng/day.

Table 6. Estimated uptake of carcinogenic, aromatic amines from ink (exposure scenario: hobbyists mimicking professional use; "free" amines included)

Amine	*Route of exposure*	*Amount (μg/g)*	*Fraction taken up*	*Product weight (g)*	*$E_{eff,total\ amine}$ (μg)*	*Duration of product cycle (years)*	*No. of life-time product cycli*	*Life-long amine uptake (ng/day)*
3,3'-Dichlorobenzidine	Inhalatory	340	$2.7 \cdot 10^{-4}$	120	10.9	1	10	4.3
	Dermal	340	$3.2 \cdot 10^{-4}$	120	12.9	1	10	5.0
o-Toluidine	Inhalatory	170	$2.7 \cdot 10^{-4}$	120	5.5	1	10	2.2
	Dermal	170	$3.2 \cdot 10^{-4}$	120	6.5	1	10	2.5

APPENDIX 2 CALCULATION OF NRLS ON THE BASIS OF TD_{50} VALUES

Starting with a TD_{50} of 1,7 mg/kg/day for benzidine the life-long exposure which leads to 1 extra case of cancer in one million life-long exposed persons, i.e. the NRL, corresponds with $10^{-6}/0{,}5 \cdot 1{,}7 \cdot 10^{6} = 3.4$ ng/kg/day. For an adult weighing 70 kg this corresponds with 238 ng benzidine/day. Analogously, TD_{50} values of 30 mg/kg/day for *o*-anisidine, 2-4 mg/kg/day for 2,4-toluenediamine, 7 mg/kg/day for 4,4'-diaminodiphenylmethane, 28 mg/kg/day for 3,3'-dichlorobenzidine and 44 mg/kg/day for *o*-toluidine lead to NRLs of 60 ng/kg/day (adult exposure: 4200 ng/day), 4-8 ng/kg/day (adult exposure: 280-560 ng/day), 14 ng/kg/day (adult exposure: 980 ng/day), 56 ng/kg/day (adult exposure: 3920 ng/day) and 88 ng/kg/day (adult exposure: 6160 ng/day).

APPENDIX 3

CONSEXPO report 1

Generated by CONSEXPO 3.NT test on 22-12-1999

Compound:o-toluidine(CAS: 000095-53-4)
Subject: person
Weight: 70.000 kg (uninspected default)

CONTACT

Contact scenario: user defined
Parameter definition of scenario:
Duration of contact per event: 90.000 min
Duration of actual use per event: 60.000 min
Frequency of contact: 4.000 1/month
Start of contact: 0.00e+00 min

INHALATION

Exposure
Scenario: spray: well mixed model
Person uses product (room volume, ventilation and release area personal).
Personal volume=1.000000 m3.
Mean event concentration (average case): 7.973e-05 mg/m3
Year average (average case): 6.548e-07 mg/m3
Mean event concentration (cumulative worst case): 7.973e-05 mg/m3
Year average (cumulative worst case): 6.548e-07 mg/m3

Exposure estimates based on the following parameters:
Generation rate: 42.000 mg/min
Weight fraction: 1.70e-04 fraction
Airborne fraction: 5.000 %
Droplet size: 50.000 micrometer
Release height: 150.000 cm
Room volume: 20.000 m3
Ventilation rate: 12.000 m3/hr

Uptake
Model: fraction model
Average case estimate: 0.000e+00 mg/year
: 0.000e+00 mg/(kg.day)
Cumulative worst case estimate: 0.000e+00 mg/year
: 0.000e+00 mg/(kg.day)

Uptake estimates based on the following parameters:
Absorbed fraction: 1.000 fraction
Inhalation rate: 25300.000 cm3/min
Respirable fraction: 0.00e+00 fraction

DERMAL

Exposure
Scenario: contact rate
Mean event concentration during use (average case): 1.133e-01 mg/cm3
Year average (average case): 9.309e-04 mg/cm3
Mean event concentration during use (cumulative worst case): 1.133e-01 mg/cm3
Year average (cumulative worst case): 9.309e-04 mg/cm3

Exposure estimates based on the following parameters:
Contact rate: 0.210 mg/min
Weight fraction: 1.70e-04 fraction
Product density: 1.000 g/cm3

Uptake
Model: fraction model
Average case estimate: 1.028e-02 mg/year
: 4.021e-07 mg/(kg.day)
Cumulative worst case estimate: 1.028e-02 mg/year
: 4.021e-07 mg/(kg.day)
Uptake estimates based on the following parameters:
Absorbed fraction: 0.100 fraction

ORAL

Exposure
Scenario: nonrespirable fraction from inhalatory exposure
Mean event concentration (average case): 7.973e-11 mg/cm3
Year average (Average case): 6.548e-13 mg/cm3
Mean event concentration (cumulative worst case): 7.973e-11 mg/cm3
Year average (cumulative worst case): 6.548e-13 mg/cm3

Exposure estimates based on the following parameters:
Conform inhalatory exposure model.

Uptake
Model: fraction model
Average case estimate: 8.714e-03 mg/year
: 3.408e-07 mg/(kg.day)
Cumulative worst case estimate: 8.714e-03 mg/year
: 3.408e-07 mg/(kg.day)

Uptake estimates based on the following parameters:
Absorbed fraction: 1.000 fraction

TOTAL DOSE

Average case
(Semi)chronic dose 7.430e-07 mg/kg bw/day (year averaged)
Acute dose 5.653e-06 mg/kg bw/day of application
Cumulative worst case
(Semi)chronic dose 7.430e-07 mg/kg bw/day (year averaged)
Acute dose 5.653e-06 mg/kg bw/day of application

CONSEXPO report 2

Generated by CONSEXPO 3.NT test on 22-12-1999

Compound: 3,3'-dichlorobenzidine (CAS: 91-94-1)
Subject: person
Weight: 70.000 kg (uninspected default)

CONTACT

Contact scenario: user defined
Parameter definition of scenario:
Duration of contact per event: 90.000 min (uninspected default)
Duration of actual use per event: 60.000 min (uninspected default)
Frequency of contact: 48.000 1/year (uninspected default)
Start of contact: 0.00e+00 min (uninspected default)

INHALATION

Exposure
Scenario: spray: well mixed model
Person uses product (room volume, ventilation and release area personal).
Personal volume=1.000000 m3.
Mean event concentration (average case): 1.595e-04 mg/m3
Year average (average case): 1.310e-06 mg/m3
Mean event concentration (cumulative worst case): 1.595e-04 mg/m3
Year average (cumulative worst case): 1.310e-06 mg/m3

Exposure estimates based on the following parameters:
Generation rate: 42.000 mg/min
Weight fraction: 3.40e-04 fraction
Airborne fraction: 5.00e-02 fraction
Droplet size: 50.000 micrometer
Release height: 150.000 cm
Room volume: 20.000 m3
Ventilation rate: 12.000 m3/hr

Uptake
Model: fraction model
Average case estimate: 0.000e+00 mg/year
: 0.000e+00 mg/(kg.day)
Cumulative worst case estimate: 0.000e+00 mg/year
: 0.000e+00 mg/(kg.day)

Uptake estimates based on the following parameters:
Absorbed fraction: 1.000 fraction
Inhalation rate: 25300.000 cm3/min
Respirable fraction: 0.00e+00 fraction

DERMAL

Exposure
Scenario: contact rate
Mean event concentration during use (average case): 2.267e-01 mg/cm3
Year average (average case): 1.862e-03 mg/cm3
Mean event concentration during use (cumulative worst case): 2.267e-01 mg/cm3
Year average (cumulative worst case): 1.862e-03 mg/cm3

Exposure estimates based on the following parameters:
Contact rate: 0.210 mg/min
Weight fraction: 3.40e-04 fraction
Product density: 1.000 g/cm3

Uptake
Model: fraction model
Average case estimate: 2.056e-02 mg/year
: 8.043e-07 mg/(kg.day)
Cumulative worst case estimate: 2.056e-02 mg/year
: 8.043e-07 mg/(kg.day)

Uptake estimates based on the following parameters:
Absorbed fraction: 0.100 fraction

ORAL

Exposure
Scenario: nonrespirable fraction from inhalatory exposure
Mean event concentration (average case): 1.595e-10 mg/cm3
Year average (Average case): 1.310e-12 mg/cm3
Mean event concentration (cumulative worst case): 1.595e-10 mg/cm3
Year average (cumulative worst case): 1.310e-12 mg/cm3

Exposure estimates based on the following parameters:
Conform inhalatory exposure model.

Uptake
Model: fraction model
Average case estimate: 1.743e-02 mg/year
: 6.816e-07 mg/(kg.day)
Cumulative worst case estimate: 1.743e-02 mg/year
: 6.816e-07 mg/(kg.day)

Uptake estimates based on the following parameters:
Absorbed fraction: 1.000 fraction

TOTAL DOSE

Average case
(Semi)chronic dose 1.486e-06 mg/kg bw/day (year averaged)
Acute dose 1.131e-05 mg/kg bw/day of application
Cumulative worst case
(Semi)chronic dose 1.486e-06 mg/kg bw/day (year averaged)
Acute dose 1.131e-05 mg/kg bw/day of application

Mailing list

1. Directeur Stoffen, Veiligheid en Straling
2. Drs. A.W. van der Wielen, VROM/ DGM/SVS/SN
3. Drs. E. Siebel, VROM/DGM/SVS/SN
4. Drs. J. Groos, VROM/DGM/SVS/SN
5. Dr. F.O. Dorgelo, VROM/DGM/SVS/SN
6. Dr. Ir. P.C. Bragt, VWS/ST.TZ/W en V
7. Drs. G. E.H. Houben, VWS/GZB/CO
8. Dhr. D.H. Meijer, VWS/ST.TZ/W en V
9. Dr. H. Roelfzema, VWS/GZB/CO
10. Ir. A.M. Bongers, SZW/ARBO
11. Drs. F.M. van Buul, VROM/DGM/ICB
12. Drs. Neudecker, VROM/DGM/A/PIVA
13. Mr. F.E. Hes, VROM/ VHCP
14. Dr. E.D. Kroese, TNO Voeding
15. Drs. C. Nauta, VROM/ HIMH
16. Dr. S. Carter, Laboratory of the Government Chemist, UK.
17. Dr. A.S.A.M. van den Burght, Gezondheidsraad, Den Haag
18. Dr. H. Wallin, National Institute of Occupational Health Denmark
19. Dr. A. Wennemer, TÜV Rheinland Sicherheid und Umweltschutz
20. Dr. Th. Platzek, Bundesinstitut für gesundheitlichen Verbraucherschütz und Veterinärmedizin
21. Prof. Dr. I.C. Shaw, Centre for Toxicology, University of Central Lancashire, UK
22. Dhr. H.R. Reus, Regionale Dienst Noord
23. Ir. A. Fluitman, CREM
24. Ir. J. Mensink, CREM
25. Drs. A. Klingenberg, Inspectie-Milieuhygiëne-Zuid-Holland Regionaal
26. R Luijk, Consumentenbond, Den Haag
27. Ir H. Veurtjes, Veurtjes Consultancy & Counseling
28. Dr. E. A. Clarke, Ecological and Toxicological Assocation of Dyes and Organic Pigments (ETAD)
29. Dr. W. ten Berge, DSM
30. Ir. E. Claeys, CIBA-GEIGY Maastricht b.v.
31. Dr. R. Geenen, TNO-MEP
32. Mr. Ch. van der Horst, BASF Nederland b.v.
33. Vereniging van de Nederlandse Chemische Industrie
34. Dr. H. Motchi, Ecological and Toxicological Assocation of Dyes and Organic Pigments (ETAD)
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38. Dr. A. Opperhuizen, Hoofd LEO
39. Dr. W.H. Könemann, Hoofd CSR
40. Dr. J. de Bruijn, RIVM/CSR
41-46. Auteurs
47. SBD/Voorlichting en Public Relations
48. Bureau rapportenregistratie
49. Bibliotheek RIVM
50-66. Bureau rapportenbeheer
67. Archief LBM
68-88. Reserve exemplaren