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Health Risk Assessment for Organotins in Textiles

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Abstract

In January 1998 RIVM was asked to carry out a preliminary risk assessment on organic tin compounds (organotins) in textiles. Measurements carried out by the Dutch Health Protection Inspectorate had shown these potentially toxic compounds to be present in several consumer products, including items of clothing worn by adults and children and hygiene products for women and infants. The initial assessment of this problem by RIVM (dated March 1998) was used in the ongoing discussions between the Health Inspectorate and industry. At an early stage in these discussions industry indicated the sources of organotin contamination to have been located and subsequently removed from the production process, thus reducing the issue under investigation to the question of whether there had been a risk for consumers at the time when the contamination was still in place (historical risk). In addition, industry provided further information that could be used to improve on the initial risk assessment. These new data largely cleared up the points of concern noted in our preliminary risk assessment. Some data limitations remain but overall the conclusion is that most likely the contaminated items did not pose any health risk for the consumers using them.

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Samenvatting

In opdracht van de Inspectie Gezondheidsbescherming Waren en Veterinaire Zaken van het Ministerie van Volksgezondheid, Welzijn en Sport hebben we een risicobeoordeling gemaakt voor organische tinverbindingen (organotins) in textiel. In een serie chemische analyses uitgevoerd door de Inspectie in consumentenproducten zoals pantalons, ondergoed, luiers en hygienische verzorgingsproducten voor vrouwen was gebleken dat deze regelmatig verontreinigd zijn met organotins. Onze eerste voorlopige beoordeling van dit probleem verscheen in maart 1998. In overleg tussen de Inspectie en de industrie werd informatie uitgewisseld en werden additionele gegevens verschaft die gebruikt konden worden in de definitieve risicobeoordeling in deze zaak. Al in een vroege fase van dit overleg is door de industrie aangegeven dat de bronnen van de verontreiniging opgespoord en vervolgens geëlimineerd zijn. Daarmee was de vraagstelling teruggebracht tot de beoordeling of er sprake was van een risico in de periode dat de verontreiniging nog wel aanwezig was (historisch risico). Gebruikmakend van de nieuwe gegevens werd de risicobeoordeling geactualiseerd wat leidde tot de definitieve versie vastgelegd in het huidige rapport.

Organotins zijn een in chemisch opzicht diverse groep van potentieel toxische verbindingen. Een opvallende toxicologische eigenschap van de organotins is de toxische werking die ze hebben op het immuunsysteem, een effect dat zowel door de dialkyltins, trialkyltins als de trifenyltins veroorzaakt wordt. Voor wat betreft de blootstelling aan organotins kan een *event*-specifieke expositie en een mogelijke totale expositie over langere duur onderscheiden worden. De laatste kan gebruikt worden om het risico voor nadelige effecten op interne organen te evalueren door vergelijking met een chronische grenswaaarde. Event-specifieke effecten die zich kunnen voordoen zijn locale huidirritatie en sensibilisatie (op de plaats van contact met de huid).

We hebben de maximaal mogelijke expositie bepaald (in mg/kg lichaamsgewicht/dag) voor elk van de verontreinigde producten. De aanname daarbij was dat in de producten altijd de maximumconcentratie zoals gevonden in de chemische analyses aanwezig was. De resulterende *worst case*-schatting hebben we vervolgens vergeleken met de chronische grenswaarde (de *tolerable daily intake*, TDI). Waar TDIs overschreden werden (wat erop wijst dat er mogelijk een gezondheidsrisico is) werd de expositiesituatie nader geanalyseerd om te komen tot een verbeterde schatting van de blootstelling. Daarbij konden we gebruik maken van de nieuwe data ingeleverd door de industrie in het kader van overleg over deze kwestie. De kans op event-specifieke effecten werd geevalueerd op basis van wat er bekend is over de potentie van de verschillnede organotins om huidirritatieen sensibilisatie te veroorzaken. Bovendien waren voor sommige van de producten testen met menselijke vrijwilligers beschikbaar waarin het intacte product werd getest.

Het resultaat van onze risicobeoordeling is dat er op enkele punten beperkingen blijven bestaan voor wat betreft de beschikbare gegevens maar overall concluderen we dat de verontreinigde items waarschijnlijk geen enkel risico vormden voor de gezondheid van de consument. Opgesplitst naar product zijn onze conclusies (betreffende het historische risico) als volgt:

Product	systemische effecten	irritatie/sensibilisatie
tampons	geen risico	waarschijnlijk geen risico
maandverband/inlegkruisjes	geen risico	waarschijnlijk geen risico
kraamverband	geen risico	waarschijnlijk geen risico
luiers	geen risico	beperkte data, waarschijnlijk geen risico
luierbroekjes	geen risico	beperkte data, waarschijnlijk geen risico
kleding[1)]	geen risico	beperkte data, waarschijnlijk geen risico
tentdoek	geen risico	beperkte data: geen conclusie mogelijk

1) Items: T-shirts, onderbroeken, trui, herenhemd, maillots, sokken.

Summary

On behalf of the Inspectorate of Health Protection, Commodities and Veterinary Public Health of the Ministry of Health, Welfare and Sports of the Netherlands, we carried out a health risk assessment for organic tin compounds (organotins) in textiles. In a series of chemical analyses of consumer products such as pants, underwear, female hygiene products and napkins (diapers), the Inspectorate had found that several of these items were contaminated with organotins. Our first preliminary risk assessment for this problem appeared in March 1998. As part of ongoing discussions between the Inspectorate and industry, information was exchanged and additional data were supplied to be included in the final assessment of the issue. Already at an early stage in these discussions industry indicated the sources of organotin contamination to have been located and subsequently removed from the production process, thus reducing the issue under investigation to the question of whether there had been a risk for consumers at the time when the contamination was still in place (historical risk). Using the newly supplied data our preliminary risk assessment was updated leading to the final version that is contained in the present report.

Organotins are a chemically diverse group of potentially toxic compounds. A salient toxicological feature of the organotins is their toxicity to the immune system, an effect that is produced by the dialkylins, trialkyltins as well as triphenyltins. As to organotin exposure due to contact with contaminated textiles, an event-specific exposure and a possible total exposure over longer periods of time may be distinguished. The latter may be used to evaluate the risk for adverse effects on internal organs (systemic effects) by comparison with a long-term limit value. Event-specific effects that may occur are skin irritation or sensitization at the site of contact.

We determined the maximum possible exposure (as mg/kg bw/day) for each of the organotin-positive items. For this we assumed that the items consumed always contained the maximum concentration as observed the chemical analyses. The worst-case estimate thus obtained was compared to the chronic limit value (the tolerable daily intake, TDI) for the compound in question. Where TDIs were exceeded (which indicates that there may be a health risk) the exposure situation was analysed in more detail in order to determine if an improved estimate of exposure was possible. For this the data newly supplied by industry in the course of the discussions on this topic could be used. The likelihood of event-specific effects was evaluated using data on the potential of the different organotins to produce skin irritation or sensitization. In addition, for some of the items skin tests in human volunteers in which whole products were tested, were available.

The outcome of the risk assessement is that some data limitations remain but overall the conclusion is that most likely the contaminated items did not pose any health risk for the

consumers using them. Per product our risk assessment conclusions (pertaining to the historical risk) were as follows:

Product	systemic effects	irritation/sensitization
tampons	no risk	probably no risk
sanitary pads	no risk	probably no risk
maternity sanitary pads	no risk	probably no risk
napkins	no risk	limited data, probably no risk
pilches	no risk	limited data, probably no risk
clothing[1)]	no risk	limited data, probably no risk
canvas	no risk	limited data: no conclusion possible

1) Items: T-shirts, underpants, sweater, shirts, tights socks.

1. INTRODUCTION

In 1997 the Inspectorate for Public Health/Food Inspection Department in Groningen performed a series of measurements of the concentrations of organotins in textile products. The results of these measurements have been reported by Alberts and Dannen (1997). These authors state that the presence of organotins in the textile products sampled is a result of the use of these substances as biocides for the stock protection of natural fibres (trialkyltins and triaryltins) and as stabilisers in PVC (dialkyltins and diaryltins).

The report of Alberts & Dannen (1997) focusses on the following organotins: dibutyltins, tributyltins, dioctyltins, trioctyltins, diphenyltins[1] and triphenyltins. The same report also contains a brief survey of the physicochemical properties of these organotins. For the problem dealt with in the current report it is relevant to know that the organotins are only slightly volatile and that they are not water-soluble but are freely soluble in organic diluents. Because of the low volatility we estimate that inhalation exposure of consumers will be negligible when organotins are present in clothes or other textiles. The hydrofobicity of the organotins indicates that penetration of skin and mucous membranes is possible during contact with contaminated textile products.

The present report is the follow-up to our preliminary risk assessment that was previously reported. In his letter from January 12, 1998 Dr. Bragt of the Health Protection Inspectorate requested the RIVM/CSR to carry out a preliminary risk assessment on organotins in textiles, the goal of which was to determine whether the problem needed a more in-depth risk assessment. Our preliminary risk assessment report was sent to Dr. Bragt in March 1998. Subsequently this report was discussed with industry on June 26, 1998 and again on September 11, 1998 and September 14, 1999. In these meetings industry provided new data to be included in the final assessment of this problem. In addition, already at an early stage industry indicated the sources of organotin contamination to have been located and subsequently eliminated from the production process. In the meetings it was agreed upon that the only problem that would still need attention is the assessment of whether there was a risk for consumers at the time when the contamination was still in place (historical risk). In the present report this question is addressed, now also using the additional material that was provided by industry since our preliminary risk assessment.

Below in Chapter 2 the exposure assessment we have developed for this report is discussed briefly. More detailed information on the exposure calculations is given in Appendix 1. In Chapter 3 the use that we made of toxicity data in the present risk assessment is explained

and the relevant toxicological information is briefly summarized. More detailed information on the toxicity of the different organotins is presented in Appendix 2 through 4. In Chapter 4, finally, the risk assessment is given for the individual items in which Alberts and Dannen found organotins in their series of measurements. These items were:

- tampons;
- sanitary pads;
- maternity sanitary pads;
- napkins;
- pilches;[2]
- plastic bags;
- clothing (T-shirts, underpants, shirts, tights, socks);
- sailing cloth;[3]
- canvas.[4]

In sections 4.1 through 4.7 it is determined whether the levels of organotins that Alberts and Dannen found in these items might present a risk to the consumers that use them. In this risk assessment the newly supplied data that were not available at the time of writing our preliminary risk assessment are included. Chapter 5 provides an overview of the risk assessment conclusions.

As to the general approach chosen in the present risk assessment it should be noted that the procedure used involves two basic steps: first a worst-case estimate is made as an initial screening and only if this exercise indicates a possible problem further analysis of the data on exposure or toxicity is carried out in order to refine the risk assessment. In the chapters that follow this sequence of two steps (i.e. preliminary risk assessment followed by refinements only if necessary) will be encountered for several of the products discussed.

[1] The diphenyltins were not found in any of the textile products sampled by Alberts & Dannen and for that reason will not be discussed further in the present report. It may be added here that for the diphenyltins no toxicity data are available.

[2] In Dutch: luierbroekjes.

[3] In Dutch: zeil.

[4] In Dutch: tentdoek.

2. EXPOSURE ASSESSMENT

When humans are exposed to organotins due to contact with contaminated textile products, direct effects on the site of contact (irritation or sensitization of skin or mucous membranes) may occur. In addition, absorption of the organotins into the body, leading to exposure of internal organs, may produce toxic effects (systemic toxicity). Thus, in the exposure assessment both the immediate local exposure (contact concentration) and the systemic exposure are important. Since consumers use the products that were found to contain organotins regularly and frequently - sometimes more products per day - exposure over longer periods of time is possible. For the present problem we may distinguish between an "event-specific" exposure and a possible total exposure over longer periods of time. The latter is the mean amount of the contaminant absorbed into the body, expressed as mg/kg body weight/day, using an averaging time of one year. In Appendix 1 calculations are presented to provide an estimate of the long-term body burden of organotins for the different items of textiles examined by Alberts and Dannen (1997).

It should be noted that the levels as calculated in Appendix 1 indicate the maximal systemic exposure that is possible. This is a worst-case estimate because it was assumed that the total amount of contaminant present in the product enters the body. This is clearly an overestimation of the real exposure because part of the contaminants will not be available for absorption (i.e. will remain in the matrix of the product) or will not penetrate the skin (the skin acts as a barrier). Where such a worst-case estimate indicates that there is no risk, the problem need not be further evaluated (since even in the worst possible case no risk arises). When, however, the worst-case calculation yields exposure levels that might be harmful the problem needs closer inspection. The appropriate step to take then is to estimate the reduction in absorption due to retention of contaminant in the matrix in which it is present and, in addition, to correct for incomplete dermal absorption (barrier function of the skin). In this way a more realistic exposure estimate may be derived and it may be determined whether there really is a risk.

Estimating the event-specific exposure (contact concentration) requires a more detailed analysis than does the systemic long-term exposure. In the present case, there are insufficient data for a detailed estimate of the event-specific exposure. Nevertheless the data as now available do provide some relevant evidence on the point of the possibility of event-specific exposure leading to direct effects. This information is presented in the sections where the individual products are dealt with - see Chapter 4. Apart from these data, the results of standard toxicological studies on skin irritation and sensitization carried out with individual organotins can of course be used to assess the risk for direct effects at the site of contact with the body. In Chapter 3 it is indicated for which compounds of those found by Alberts &

Dannen (1997) such irritation and sensitization data are available and in Chapter 4 this information will be used in the risk assessment.

The discussion above refers to the dermal exposure route. Oral exposure is also possible, for example when young children suck their clothing. As stated already, the exposure calculations as presented in Appendix 1 are the maximal systemic exposure that is possible. Any oral exposure that may occur is already included in the figures calculated in Appendix 1.

The exposure calculations from Appendix 1 lead to the following figures for the maximum possible systemic exposure for the different items:

Table 1. Maximum possible systemic exposure levels to organotins based on the data of Alberts & Dannen.

	estimated maximum of exposure in µg /kg body weight/day				
product	dibutyltin	tributyltin	dioctyltin	trioctyltin	triphenyltin
tampons	0.18				
sanitary pads			0.77		
sanitary pantiliners			4.5		
maternity sanitary pads			0.10		
napkins[1)]			28		
pilches[1)]	14				12
clothing [2)]	0.003	0.31	0.41	0.025	
canvas[3)]	0.12	0.18			

[1)] Calculated for 5 kg child (for details see Appendix 1).

[2)] Items: T-shirts, underpants, shirts, tights, socks.

[3)] Calculated for 10 kg child (for details see Appendix 1).

Again, it should be noted that these figures represent worst-case estimates only to be used for an initial assessment. In Chapter 4, in order to more realistically estimate the risk, we introduce a refinement of the exposure estimate for sanitary pads, pantiliners, napkins and pilches thus showing that the above figures for these items indeed overestimate the exposure as it may have occurred in real-life situations.

3. TOXICOLOGY

As already mentioned in Chapter 2, the dermal and oral routes are of importance for the current problem. Both local and systemic effects may occur. In particular, effects on the skin/mucous membranes (irritation and sensitization) appear important because intense contact with the skin or mucous membranes may be expected to occur with several of the items sampled (sanitary pads, tampons, napkins). In Appendices 2 through 4 selected toxicity data on the organotins are presented, including data on the potential of the organotins to produce skin irritation and sensitization, as well as information on the degree of absorption (oral, dermal). The data as presented in these appendices were selected from existing toxicity reviews as available for the different groups of organotins.

From the toxicological data available for the **dialkyltins** (summarized in Appendix 2) the following conclusions are drawn:

- there are no data available with regard to the degree of absorption (dermal, oral) of the dialkyltins;
- the induction of immunotoxicological effects (suppression of thymus-dependent functions) by dialkyltins after oral administration has been demonstrated unequivocally;
- the NOAEL of 0.72 mg/kg body weight/day derived from a 2-year study in rats (dioctyltin) may be considered a preliminary NOAEL for the immunotoxic effect of the dialkyltins;
- no usable data with regard to the skin effects of the dialkyltins after dermal contact were found in the available toxicity reviews;
- the TDI of 2.3 μg/kg body weight (derived for dioctyltin compounds) can be used for an initial risk assessment of oral/systemic exposure to the dialkyltins.

From the toxicological data available for the **trialkyltins** (summarized in Appendix 3) the following conclusions are drawn:

- of the substances in this group, tributyltin oxide (TBTO) is the one which has been studied most extensively; no data are available for trioctyltins;
- the limited data available for other tributyltins indicate an effect comparable to that of TBTO;
- TBTO is absorbed by the skin (absorption percentage 10 to 15%)
- for TBTO absorption percentages of 25 to 50% are given for the oral route;
- TBTO is strongly irritating for the skin; a NOAEL (concentration or dose level without effect) for this is lacking (lowest known effect level: 10 mg/litre);
- limited data indicate that TBTO does not have a sensitizing effect on the skin;
- the performed experiments do not indicate any genotoxicity or carcinogenicity by TBTO;

- data from a large number of oral toxicity studies show that TBTO has an immunotoxic effect (suppression of thymus-dependent immune functions); the chronic NOAEL for this is 0.025 mg/kg body weight/day;
- the TDI of 0.25 μg/kg body weight (derived for TBTO) can be used for an initial assessment of risk following oral/systemic exposure to the trialkyltins.

From the toxicological data available for the **triphenyltins** (summarized in Appendix 4) the following conclusions are drawn:

- triphenyltins are absorbed by the skin (absorption percentage 55%; 30% reaches the systemic circulation);
- the average absorption percentage for the oral route is 40%;
- the available data indicate that triphenyltins have no or hardly any irritating effect on the skin (even with very high concentrations, there is no effect or only a weak effect);
- triphenyltins may have a sensitizing effect on the skin (conflicting results); the dose response relation for this potential effect is unknown;
- on the basis of the experiments performed, triphenyltins are not considered carcinogens acting through a genotoxic mechanism;
- triphenyltins are immunotoxic (suppression of thymus-dependent immune functions); the corresponding NOAEL is 1 mg/kg body weight/day in mice and 1.7 mg/kg body weight/day in rats;
- the ADI 0.5 μg/kg body weight is applicable for an initial risk assessment of oral/systemic exposure.

In the following chapter the toxicity data are used to evaluate the risk posed by the presence of organotins in textiles, based on the concentrations reported by Alberts & Dannen. This is done separately for each of the products in which organotins were present. For some of the products additional toxicity data are available, i.e. tests on skin effects in human volunteers. These studies were carried out, not with individual organotins but with the whole product in which organotins were present as contaminants. These data will be introduced in the section of Chapter 4 dealing with the product in question.

To end the present chapter, a remark on the way we have used the TDIs for the individual organotins. In the risk assessment as presented in the next chapter the risk for systemic toxicity produced by any organotin compound is determined by comparing the TDI for the compound in question with the estimated systemic exposure that is the result of dermal contact. The TDI is derived from oral toxicity data. When the TDI is compared with the dose level thought to have entered the body via the dermal route (as we do in the next chapter) ideally a correction should be made for incomplete absorption via the oral route: the comparison should be based on the so-called ‘internal dose’ (the part of the externally applied dose that reaches the blood). For tributyltins and triphenyltins such a correction is possible;

for the other organotins this is not possible due to lack of data. As will be seen in the next chapter we have made such a correction only for the item ‘tributyltins in clothing’ (section 4.6). For none of the other items and contaminants such a correction was made. In these cases the approach now chosen implies the assumption that dermal penetration is equal to oral absorption, which most likely is a relative overestimation of the dermal uptake because for most chemicals dermal absorption is lower than oral absorption.
A further correction that would ideally have to be made when using orally derived TDI for uptake via the dermal route is for difference in biotransrmation and elimination between these routes. Such a correction requires more detailed information on these topics than is available for the organotins and therefore is not feasible for the problem under investigation.

4. RISK EVALUATION

4.1 Tampons

In tampons Alberts & Dannen found dibutyltins in concentrations up to 1.3 mg/kg. The maximum possible systemic exposure as a result of women using contaminated tampons is 0.18 μg/kg body weight/day (taken from Table 1). The TDI to be used is 2.3 μg/kg body weight (derived for dioctyltins). Thus, the maximum possible systemic exposure is well within the TDI which leads to the conclusion that use of organotin contaminated tampons posed no risk for systemic toxicity.

As to possible local effects (irritation or sensitization of skin or mucous membranes) relatively few data are available. No studies on the skin irritating and skin sensitizing potential of the dibutyltins are available (see Appendix 2). After the meeting of September 1998 industry submitted additional data. A summary of results of three studies with human volunteers was provided. In these studies tampons or tampon cover was tested in which organotins are assumed to be present (because these tests were done with tampons produced before the sources of organotins were eliminated from the production process, the tested products are thought to have had the contaminants in them). In a study from 1990 for sensitization in which tampon cover was applied under occlusion to the skin of the back of 213 subjects on 3 days/week for three weeks (induction phase) followed by a challenge application 17 days later, no irritation or sensitization was observed (Kimberly-Clark Co., 1998a). Two further tests were done in female volunteers. These were clinical use-tests in which the cervix and vagina of women were examined with a colposcobe (an instrument inserted into the vagina for examination of the tissues with a magnifying lens) before their menstrual period. The subjects then wore the tampons and were again examined internally after the menstrual period had ended. The first of these studies dates from 1990 and was done in 215 women and the second was done 1993 in 208 women. In both cases the result was negative: no signs of irritation or inflammation were seen (Kimberly-Clark Co., 1998b). Our evaluation of these studies is as follows. Clearly these results are relevant for the problem under investigation but since it is not known what were the levels of organotins present in the items tested in these studies (the possibility that these levels were considerably lower than the maximum found by Alberts & Dannen cannot be ruled out) we think they do not provide fully conclusive evidence. Nevertheless we accept these data as an indication that tampons contaminated with organotins at the levels present before the sources of contamination were eliminated do not produce adverse effects in consumers using them. In conclusion, the limited evidence that is available indicates there to have been no risk for local effects for tampons.

4.2 Sanitary pads and pantiliners

In sanitary pads Alberts & Dannen found dioctyltins in concentrations of up to 5.2 mg/kg. The maximum possible systemic exposure as a result of women using this product is 0.77 μg/kg body weight (taken from Table 1). The relevant TDI is 2.3 μg/kg body weight (derived for dioctyltins). Thus, the maximum systemic exposure is below the TDI, showing the absence of a risk for systemic toxicity when consumers used the product that was contaminated with organotins.

In sanitary pantiliners Alberts & Dannen found dioctyltins in concentrations up to 33.1 mg/kg. The maximum possible systemic exposure as a result of women using this product is 4.5 μg/kg body weight/day (taken from Table 1). The relevant TDI is 2.3 μg/kg body weight (derived for dioctyltins). Thus, the maximum systemic exposure is above the TDI, indicating that there may have been a risk and a more detailed analysis of the exposure situation that arises when this product is used, is warranted. For sanitary pads so-called 'rewet' data have been submitted by Proctor & Gamble (1998). In tests in which the amount of fluid that resurfaces from loaded pads under pressure was determined, it is was found that 2-4% of the fluid resurfaces. Based on the rewet maximum a reduction factor of 25 may be introduced for the exposure estimate for sanitary pads and pantiliners. This leads to an estimated systemic exposure level of 0.18 μg dioctyltin/kg body weight/day for sanitary pantiliners. This level is below the TDI of 2.3 μg/kg body weight. Thus correcting for incomplete 'rewet' leads to the conclusion that the real exposure was well within the TDI showing that there was no risk for systemic toxicity for consumers that wore pantiliners containing organotins as contaminants. Since women frequently use both sanitary pads and pantiliners the total exposure to dioctyltin may be calculated (summing the figures for pads and pantiliners).[5] The total exposure is about 1.0 μg/kg body weight/day, i.e. below the TDI showing there to have been no risk for systemic toxicity when both contaminated pads and pantiliners were used.

As to possible local effects (irritation or sensitization of skin or mucous membranes) the situation is as follows. No studies on the skin irritating and skin sensitizing potential of the dioctyltins are available (see Appendix 2). Among the data submitted by industry after the meeting of September 1998 were studies on skin irritation and sensitization in human volunteers using pads and pantiliners in which organotins probably were present as contaminants (because these tests were done with products produced before the elimination of the sources of organotins from the production process, the tested products are thought to have had the contaminants in them). The test for skin irritation was a 21-day study in which sample patches of the pads and pantiliners were applied to the back of 25 human volunteers 23 hours/day for 21 days. No irritation was seen (Kimberley-Clark Co., 1998b). Skin

[5] Note that in this estimate the figure for sanitary pads has not been corrected for incomplete rewet (even without using this correction step is can be concluded that there is no risk).

sensitization was studied in 200 volunteers using the Human Repeat Insult Patch Test. The induction consisted of application of patches of the pads to the back skin three times per week for three weeks. Three weeks later the challenge application was made similarly and skin reactions were recorded. No sensitization was observed (Kimberley-Clark Co., 1998b). In yet a further study in human volunteers in which again pads were tested that are thought to have been contaminated with organotins, 256 women were asked to wear sanitary pads of two types daily over a period of 8 weeks (both during non-menstruation and menstruation). Five times during this period the subjects were clinically examined for irritation and moisture (five sites covered by the pad were evaluated). No adverse reactions were observed (Hanke-Baier et al., 1994).
Similarly as with the volunteer studies with tampons (section 4.1) we feel that the results of the volunteer studies with sanitary pads, though clearly relevant for the problem under investigation, do not constitute fully conclusive evidence because the levels of organotins present in the items tested in these studies are not known (the possibility that these levels were considerably lower than the maximum found by Alberts & Dannen cannot be ruled out). Nevertheless we accept these data as an indication that pads contaminated with organotins at the levels present before the sources of contamination were eliminated do not produce adverse effects on the skin of consumers using them. In conclusion, the limited evidence that is available indicates there to have been no risk for local effects for sanitary pads and pantiliners.

4.3 Maternity sanitary pads

In maternity sanitary pads Alberts & Dannen detected dioctyltin at a concentration of 2.2 mg/kg. The maximum possible systemic exposure as a result of women using this product is 0.10 μg/kg body weight/day (taken from Table 1). The relevant TDI is 2.3 μg/kg body weight (derived for dioctyltins). Thus, the maximum systemic exposure is below the TDI, showing that there is no risk for systemic toxic effects for consumers using the pads.

As to possible local effects (irritation or sensitization of skin or mucous membranes) there is a paucity of data. No studies on the skin irritating and skin sensitizing potential of the dioctyltins are available (see Appendix 2). Additional studies in humans like those available for tampons and sanitary pads are not available for maternity sanitary pads. The exposure situation for ordinary pads however closely resembles that of maternity sanitary pads making the observation in humans for the ordinary pads relevant for maternity pads also. Thus, the conclusion drawn for ordinary pads, i.e. that the limited evidence that is available indicates there to have been no risk for local effects, also applies to maternity sanitary pads.

4.4 Napkins

In napkins (diapers) Alberts & Dannen detected dioctyltin at a concentration of up to 4.7 mg/kg.[6] In a meeting with industry held at the Health Inspectorate on 14 September 1999 at which Dr. Dannen was present it was concluded that the organotin contamination in napkins and pilches was present not in the whole product (as previously assumed) but only in the tape system used for fastening the product. The concentrations in the attachments strips were estimated to be 10 times higher than the figures presented originally by Alberts & Dannen for the entire napkins and pilches (personal communication by F. Dannen of the Health Inspectorate and F. Koelewijn of Kimberly-Clark Europe). Maximum systemic exposure for consumers wearing napkins with organotin contaminated attachment tape is 28 micrograms DOT/kg body weight/day (taken from Table 1; see Appendix 1 for explanation). With proper use of the product, however, no contact between the skin and the tape strip will occur and no systemic exposure will be possible. It was agreed at the 14 September meeting to use a skin contact area of 1 cm^2 to take into account any inadvertent (infrequent) contact of the attachment tape with the skin. The total surface of the tape system was estimated to be about 40 cm^2 and the use of a contact surface of 1 cm^2 was taken to imply a reduction of exposure by a factor of 40. Taking this into account leads to a systemic exposure as a result of infants wearing contaminated napkins of 0.7 μg/kg body weight/day. The relevant TDI is 2.3 μg/kg body weight (derived for dioctyltins). Thus, the estimated systemic exposure is below the TDI showing there to have been no risk for systemic toxicity for this item.

As to possible local effects (irritation or sensitization of skin or mucous membranes) there is a paucity of data. No studies on the skin irritating and skin sensitizing potential of the dioctyltins are available (see Appendix 2). Additional studies in humans like those available for tampons and sanitary pads have not been submitted for napkins. As explained above, in the contaminated napkins the organotins were present in the tape system used for fastening the product. With proper use of the product there will be no contact with the skin and consequently no risk for local effects. Any inadvertent contact of the tape with the skin might lead to skin effects but such effects would be immediately visible and the person taking care of an infant showing this kind of effect most likely will immediately stop using the product in question or seek medical advice to determine the cause of the problem. Thus, the risk for local effects presumably will have been limited.

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[6] According to industry (information provided at the meeting of September 11, 1998) what was present in the napkins was *in*organic tin instead of organic tin (thus, the validity of chemical analysis carried out by Alberts and Dannen was questioned). We have contacted Dr. Bragt again on this issue. According to information provided by Dr. Dannen the original samples did contain organotins; this was confirmed by another test laboratory (Personal communication by Dr. Bragt, December 10, 1998). In a further meeting with industry held on September 14, 1999 it was agreed by all parties that the original chemical analyses as reported by Alberts & Dannen (1997) were done correctly and that what they measured indeed were organic tin compounds.

4.5 Pilches

In pilches Alberts & Dannen detected triphenyltin at a concentration of up to 1.7 mg/kg and dibutyltins at a maximum of 2.0 mg/kg. As was concluded in the meeting with industry held on September 14, 1999 in pilches organotins were present in the tape system only with the concentrations being about 10 times as high as originally reported. This leads to a maximum possible systemic exposure to triphenyltin as a result of infants wearing the product of 12 µg/kg body weight/day (taken from Table 1). Assuming a reduction of 1/40 for incomplete skin contact (as was done in paragraph 4.4 for napkins - this was agreed upon at the meeting with industry of September 14, 1999) this leads to an estimated systemic exposure of 0.3 µg/kg body weight/day. The relevant TDI is 0.5 µg/kg body weight. For dibutyltin the maximum possible exposure is estimated at 14 µg/kg body weight/day (Table 1). Taking into account the reduction for incomplete skin contact (factor 1/40) the estimated exposure is 0.35 µg/kg body weight/day. The TDI for dialkytins is 2.3 µg/kg body weight (derived for dioctyltins). Thus, for both triphenyltin and dibutyltin the estimated systemic exposure does not exceed the TDI showing there to have been no risk for systemic toxicity when the product contained the organotins.

As to possible local effects (irritation or sensitization of skin or mucous membranes) no skin irritation is expected to arise from the presence of triphenyltins because animal studies show triphenyltins to have very low potential as skin irritants. In addition, and similarly as was remarked for napkins in paragraph 4.4, when organotins are present in specific parts of the product (tape system) that do not make contact with the skin there will be no risk for local effects. Any inadvertent contact that might lead to adverse skin reactions would most likely be avoided on later occasions because the person taking care of the infant showing such reactions following contact with the contamination, would stop using the product in question or seek medical advice to determine the cause of the problem. Thus, the risk for local effects presumably will have been limited.

4.6 Clothing (T-shirts, underpants, sweaters, shirts, tights, socks)

In the different items of clothing sampled by Alberts and Dannen a number of organotins were found. In underpants for men dibutyltin was present (0.1 mg/kg). Tributyltins were found in underpants, in a T-shirt and in a sweater (maximum 9.9 mg/kg). Dioctyltins were present in a shirt, in underpants, in tights, and in a T-shirt (maximum 13.3 mg/kg). Trioctyltins were found in baby socks (0.8 mg/kg). The maximum possible exposure as a result of consumers wearing these products is 0.003 µg dibutyltin/kg body weight/day, 0.31 µg tributyltin/kg body weight/day, 0.41 µg dioctyltin/kg body weight/day, 0.025 µg trioctyltin/kg body weight/day (figures taken from Table 1). Exposure to the organotins is

assumed to have occurred one at a time (no simultaneous exposure). Comparing the maximum possible exposures with the relevant TDIs (2.3 μg /kg body weight for dialkyltins, 0.25 μg /kg body weight for the trialkyltins) shows exceedence only for tributyltin. Thus, only for tributyltin a more detailed analysis of the exposure situation is warranted. As can be seen from the information given in Appendix 3, for tributyltinoxide there are data concerning oral and dermal absorption and using these data the exposure estimate may be corrected for incomplete dermal penetration. The factor to be used for this correction is the ratio between the dermal and oral absorption percentages (10 and 25%, respectively). Thus a factor 2.5 is introduced; dividing the maximum possible exposure level as given in Table 1 by this factor gives a figure of 0.12 μg /kg body weight which is below the TDI of 0.25 μg /kg body weight. Thus, for tributyltins also there was no risk for systemic toxicity for consumers wearing the items of clothing containing the maximum amounts detected by Alberts and Dannen.

As to possible local effects (irritation or sensitization of the skin) the following remarks can be made. For trioctyltins there are no experimental data on skin irritation and skin sensitization. For tributyltins it is known that tributyltinoxide is a potent skin irritant. Skin sensitization is not known to be produced by tributyltinoxide. For skin irritation by tributyltinoxide 10 mg/litre is the lowest known effect-concentration (see Appendix 3); a NOAEL for this effect is not known. Whether or not tributyltins in clothing at concentration up to 9.9 mg/kg (the maximum found by Alberts and Dannen) will produce skin irritation cannot be determined with any certainty. That a concentration of 10 mg/litre would be present in sweat due to transfer form the contaminated piece of clothing seems unlikely given the low water solubility of the organotins.
In conclusion, the available data are insufficient for drawing firm conclusions as to how likely skin effects were when clothing was worn that contained organotins as contaminants. As already noted above adverse skin reactions, when occurring, are easily detected by consumers and normally speaking any consumer would discontinue wearing the garment in question upon discovering any adverse skin reaction.

4.7 Canvas

For canvas maximum exposure was estimated using the result of the experiment in which the surface was wiped and the amounts of dislodgeable dibutyltin and tributyltin were determined. The result was 0.12 μg dibutyltin/kg body weight/day and 0.18 μg tributyltin/kg body weight/day (taken from Table 1). Comparing these levels with the TDIs (0.3 μg/kg body weight for dibutyltin and 0.25 μg/kg body weight for tributyltin) shows the TDIs not to be exceeded. Thus, at the levels found in canvas no risk of systemic toxicity was present.

As to possible local effects (irritation or sensitization of the skin) there are very few data available. For dibutyltins there are no experimental data on skin irritation and skin

sensitization. Consequently no conclusion can be drawn as to the question if such effects might have occurred due to the contamination of canvas with dibutyltins.
For tributyltins it is known that tributyltinoxide is a potent skin irritant. Skin sensitization is not known to be produced by tributyltinoxide. For skin irritation by tributyltinoxide 10 mg/litre is the lowest known effect-concentration (see Appendix 3); a NOAEL for this effect is not known. For tributyltins a maximum of 0.40 mg/m^2 was dislodgeable by wiping (result obtained by Alberts and Dannen). Assuming that this amount is wholly dissolved in the amount of sweat that is produced by a human being in a day with the canvas would lead to a concentration of about 1 mg/litre [7]. Whether or not skin irritation may occur at this concentration cannot be decided based on the data presently available, no NOAEL being available for this endpoint (LOAEL 10 mg/litre). For the exposure situation we are dealing with, a more meaningful risk assessment would require an indication of the NOAEL for the skin irritation produced by tributyltins expressed as mg/cm^2 of skin. Such a NOAEL however is not available.
In conclusion, there are insufficient data for drawing conclusions concerning the risk of skin effects as a result of dermal contact with canvas containing dislodgeable organotins in the amounts found by Alberts and Dannen.

[7] Amount of sweat produced per day: 650 ml. Body area 19400 cm^2. It is assumed that 10% of the body makes contact with canvas. The amount of dislodgeable tributyltin of 0.40 mg/m^2 is assumed to be wiped off the canvas surface onto the skin one-to-one and to be dissolved in sweat entirely. Over 1940 cm^2 of skin 65 ml of sweat is produced in one day. Thus 77 µg would dissolve in 65 ml of sweat, giving a concentration of about 1 mg/litre. Given the low water solubility of tributyltins this calculation probably overestimates the degree to which organotins will dissolve in sweat (as explained in the text above, the amount of contaminant per cm^2 of skin would be a more appropriate measure for evaluating the present exposure situation).

5. CONCLUSIONS

In 1997 the Health Inspectorate in Groningen determined a number of textile products to be contaminated with organotins. In a meeting held in June 1998 industry stated the sources of contamination with organotins to have been located and subsequently eliminated. The present report deals with the question whether there was a health risk for consumers using textile products at the time when the contamination with organotins still was in place (historical risk). The present risk assessment was based on the maximum concentrations of organotins found by the Health Inspectorate using also the additional information supplied by industry in November 1998 and October 1999. In Table 2 the conclusions drawn for the different items are summarized.

Table 2. Risk assessment conclusions for organotins in textiles (historical risk)

Product	systemic effects	irritation/sensitization
tampons	no risk	probably no risk
sanitary pads	no risk	probably no risk
maternity sanitary pads	no risk	probably no risk
napkins	no risk	limited data, probably no risk
pilches	no risk	limited data, probably no risk
clothing[1)]	no risk	limited data, probably no risk
canvas	no risk	limited data: no conclusion possible

1) Items: T-shirts, underpants, sweater, shirts, tights socks.

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Appendix 1 Exposure calculations

ESTIMATION OF THE LONG-TERM SYSTEMIC EXPOSURE

The calculations presented below are aimed at characterizing the total systemic long-term exposure level as a result of consumer exposure to organotins through the use of textile products contaminated with these compounds. The exposure estimate is based on the maximum concentrations reported by Alberts & Dannen (1997). In a meeting with industry held at the Health Inspectorate on 14 September 1999 at which Dr. Dannen was present it was concluded that in napkins and pilches (in which di-octyltins were found) organotins were present not in the whole product (as previously assumed) but only in the tape system used for fastening the product. The concentrations in the attachment strips were estimated to be 10 times higher than the figures presented originally by Alberts & Dannen for the entire napkins and pilches (personal communication by F. Dannen of the Health Inspectorate & F. Koelewijn of the Kimberly Clark Europe).

Alberts & Dannen (1997) found organotins in several consumer products. The positive samples were found in the following product groups:

1. Sanitary pads (tampons, sanitary pads, sanitary pantiliners and maternity sanitary pads);
2. Napkins and pilches[8];
3. Plastic bags;
4. Clothing (underpants/knickers, shirts, sweaters, tights, socks);
5. Sailcloth[9];
6. Canvas[10].

Most of these consumer products are used by both children and adults. Products only used by children are napkins, pilches and children's clothes.

The exposure estimation presented below will be discussed in two steps. The first step is based entirely on the figures presented by Alberts & Dannen (1997). This exposure estimate can be characterized as a *worst case* estimate. In the second step we will present some refinements of the exposure estimate based on data and calculations submitted by industry since the meeting on this topic, held on September 11, 1998.

[8] In Dutch: luierbroekjes.
[9] In Dutch: zeil.
[10] In Dutch: tentdoek.

Exposure estimation (systemic), step 1

The report of Alberts & Dannen (1997) contains measurements indicating the concentrations, on a weight basis, of organotin compounds in consumer products and the amounts of organotin which can be obtained by wiping canvas (dislodgeable organotins). This enables calculation of the potential dermal and oral absorption.

The data concerning concentrations as reported by Alberts & Dannen (1997) are processed by the following calculation, providing an upper limit estimation of the potential absorption rate. This calculation provides the *potential absorption rate* because it is assumed, firstly, that all organotin will be released from the material and, secondly, that the whole amount will consequently be absorbed by the body.

$$U_{pot} = \frac{C_{art} * W_{art} * n}{t} \quad \text{(amount/person/time)}$$

Parameters in this equation:

1. Concentration C_{art} in the product on a weight basis;
2. Weight W_{art} of the product (or the layer containing organotin);
3. Contact frequency n (number of occurrences during the averaging period t);
4. Averaging period t (time).

With respect to the product groups mentioned above, it is assumed that the groups sanitary pads, tampons, napkins and clothing are the product groups for which the exposure can be described in the manner presented. The following exposure parameters are chosen:

Product group	**Weight**	**No. of events**	**Averaging time**	**Maximum concentration**
Sanitary pads	10 g	325	365 days	5.2 mg/kg DOT
Sanitary pantiliners	5 g	598	365 days	33.1 mg/kg DOT
Tampons	10 g	312	365 days	1.3 mg/kg DBT
Maternity sanitary pads	20 g	50[1)]	365 days	2.2 mg/kg DOT
Napkins (tape system)	0.7 g [4)]	1825[3)]	365 days	47 mg/kg DOT [5)]
pilches (tape system)	0.7 g [4)]	1825	365 days	17 mg/kg TPT; 20 mg/kg DBT [5)]
Clothing	161 g[2)]	5	365 days	13.3 mg/kg DOT; 0.1 mg/kg DBT; 9.9 mg/kg TBT; 0.8 mg/kg TOT

[1] It is assumed that 50 maternity sanitary towels are used after delivery, so the estimation refers to the year in which the delivery occurred.

[2] T-shirt.

[3] Per year during the period in which napkins are worn, 5 napkins per day.

[4] Weight of tape as indicated in a personal communication of Mr. J. Glansbeek of the NVPL to Dr. F. Dannen of the Health Inspectorate dated 11 October 1999.

[5] Concentrations 10 times those presented in the report of Alberts & Dannen. In deviation of what was previously assumed (in a previous version of the present report) in napkins and pilches organotins were present only in the tape system used for fastening the product. In a meeting with industry on 14 September 1999 it was concluded that the actual concentrations in tape would be approximately 10 times the figures originally reported.

The potential systemic exposure (in mg/day/person) by direct dermal exposure to these products is now as follows:

Exposure in mg/person/day

Product group	DBT	TBT	DOT	DPT	TOT	TPT
Sanitary pads	n.d.[1]	n.d.	0.046	n.d.	n.d.	n.d.
Sanitary pantiliners	n.d.	n.d.	0.271	n.d.	n.d.	n.d.
Maternity sanitary pads	n.d.	n.d.	0.0060	n.d.	n.d.	n.d.
Tampons	0.011	n.d.	n.d.	n.d.	n.d.	n.d.
Napkins	n.d.	n.d.	0.14	n.d.	n.d.	n.d.
Pilches	0.07	n.d.	n.d.	n.d.	n.d.	0.06
Clothing	0.00022	0.022	0.029	n.d.	0.0018	n.d.

[1] n.d.= not demonstrated in the product concerned.

These potential systemic exposure levels, expressed in micrograms/kg body weight/per day, are:

Exposure (micrograms/kg body weight/day)

Product group	DBT	TBT	DOT	DPT	TOT	TPT
Sanitary pads[1]	n.d.[2]	n.d.	0.77	n.d.	n.d.	n.d.
Sanitary pantiliners[1]	n.d.	n.d.	4.5	n.d.	n.d.	n.d.
Maternity sanitary pads[1]	n.d.	n.d.	0.10	n.d.	n.d.	n.d.
Tampons[1]	0.18	n.d.	n.d.	n.d.	n.d.	n.d.
Napkins[3]	n.d.	n.d.	28	n.d.	n.d.	n.d.
Pilches[3]	14	n.d.	n.d.	n.d.	n.d.	12
Clothing[4]	0.003	0.31	0.41	n.d.	0.025	n.d.

[1] For this product, it was assumed in the calculation that the body weight is 60 kg.

[2] n.d.= not demonstrated in the product concerned.

[3] For this product, it was assumed in the calculation that the body weight is 5 kg.

[4] For this product, it was assumed in the calculation that the body weight is 70 kg.

Dermal exposure by wiping

The wiping-test performed by Alberts & Dannen shows that organotin compounds can also be wiped off textile products. The use of a so-called "transfer factor" allows for linkage of the amount, that can be wiped off, to the dermal exposure (US-EPA, 1997). The following calculation can be used: [11]

$U_{pat} = R \times TC \times t$ (amount/person/time)

This approach will apply to the product groups canvas, sailcloth, and plastic bags. Alberts & Dannen (1997) have determined the amount that can be wiped off canvas.

The parameters in the equation are:

1. The amount that can be wiped off per surface *R*, as mentioned in the report by Albert & Dannen;
2. The transfer factor *TC* expressed as surface per time. The transfer factor indicates how large the surface area is that is wiped off per time period, thus, in combination with the amount of organotin which can be wiped off, providing the amount of organotin which comes onto the skin per time period. Assumptions have to be made for the transfer factor. The Canadian PMRA has determined the following transfer factors for the assessment of CCA salts (a mixture of copper-chrome-arsenic salts used as a wood preservative) on preserved wood: For children in the age group of 2 to 5 years a transfer factor of 1,040 cm^2/h for the fingers and 14,900 cm^2/h for the rest of the body. For children in the age group of 6 to 10 years a transfer factor of 22,630 cm^2/h is assumed for the whole body. Because the whole body will not make contact with canvas, a transfer factor for the whole body will have to be converted to correspond with the body surface actually making contact. It is assumed that 10% of the body will at some time come into contact with the canvas, a surface corresponding with half the surface of the hands, half the surface of upper arms and forearms and a quarter of the surface of the head. This gives a transfer factor of 1594 to 2263 cm^2/h, respectively, for children of 2 to 5 years of age and 6 to 10 years of age. This surface does not make contact with the canvas simultaneously. In the next point, it is assumed that 10% of the body surface mentioned will actually make contact.
3. Time period of contact with the canvas *t* (h/day). It is assumed that a camper uses his tent for 6 weeks during a one year period. This is an upper limit, however it should be borne in mind that people travelling for longer periods may stay in a tent much longer. In addition, one extra day is included for storing/handling the tent in the home situation. It is assumed that contact occurs with the canvas for 1% of this 6.14 weeks period,

[11] This calculation is made for children as the relatively highest systemic burden may be expected in their case due to their lower body weight.

taking into account that only 10% of the whole body surface mentioned above actually makes contact with the canvas. Therefore, the parameter *t* amounts to 0.01*6.14*24*7/365 = 0.028 h/day.

The following estimations are made for the maximum possible systemic exposure by wiping:

1. Children between 2 to 5 years of age. TBT: 0.4 (mg/m^2) * 0.1594 (m^2/h) * 0.028 (h/day) = 0.0018 mg/day/person; DBT: 0.28 (mg/m^2) * 0.1594 (m^2/h) * 0.028 (h/day) = 0.0012 mg/day/person.
2. Children between 6 to 10 years of age. TBT: 0.4 (mg/m^2) * 0.2263 (m^2/h) * 0.028 (h/day) = 0.0025 mg/day/person; DBT: 0.28 ((mg/m^2) * 0.2263 (m^2/h) * 0.028 (h/day) = 0.0018 mg/day/person.

Per kg body weight, these values correspond with:

1. Children between 2 to 5 years of age (assumed body weight 10 kg). TBT: 0.18 micrograms/kg body weight/day; DBT: 0.12 micrograms/kg body weight/day.
2. Children between 6 to 10 years of age (assumed body weight 20 kg). TBT: 0.13 micrograms/kg body weight/day; DBT: 0.090 micrograms/kg body weight/day.

Exposure estimation (systemic), step 2

In step 1, the exposure has been calculated using several *worst case* assumptions.
These assumptions are:

1. The organotin in the product is completely available for absorption. One of the properties of the organotins is poor water-solubility, which supports the presumption that urine and transpiration will not enhance the availability for skin contact or absorption through the skin.
2. The organotin is completely absorbed dermally. Organotins which are available for dermal absorption will only be partly absorbed by the skin because the skin acts as a barrier (correction for this aspect is possible by using the dermal and oral absorption percentages for the contaminant in question).
3. In addition to incomplete availability due to the poor-water solubility of the organotins (point 1 above) it should be noted that for most products the contaminated part of the product will make incomplete contact with the skin, thereby reducing the possibility of exposure.
4. The transfer factor adapted for CCA salts also applies to wiping organotins from canvas.

The assumption of complete availability implies that the calculations described above apply both to the dermal and the oral route. Ingestion of organotins by the oral route can occur if children suck on their clothing; Of the products mentioned in the tables above, this route is only considered important for the item ‘clothing’.
Based on the data and calculations submitted by industry since the meeting of September 11, 1998 (meeting convened to discuss the preliminary risk assesment for the present problem

that was released in March, 1998) some refinements on the above worst case estimate are possible for some of the products. For sanitary pads so-called 'rewet' data have been submitted by Proctor & Gamble (1998). In tests in which the amount of fluid that resurfaces from loaded pads under pressure was determined it was found that 2-4% of the fluid resurfaces. Based on this rewet maximum a reduction factor of 25 may be introduced for the exposure estimate for sanitary pads and pantiliners. This leads to estimated systemic exposure levels of 0.03 and 0.18 micrograms DOT/kg body weight for sanitary pads and sanitary pantiliners, respectively.

For napkins and pilches the maximum exposure levels estimated above were 28 micrograms DOT/kg body weight/day (napkins) and 12 micrograms TPT/kg body weight/day and 14 micrograms DBT/kg body weight/day (pilches).[12] As already mentioned above, for napkins and pilches the contamination with organotins is present only in the tape system used for fastening the product. In a personal communication dated 11 October 1999 Mr. J Glansbeek from the NVPL provided an estimate of the weight of the tape system and its surface. According to this estimate an entire napkin has a surface of 1225 cm^2 and the tape strip has a surface of 40 cm^2. In the meeting with industry held on 14 September 1999 it was agreed that a skin contact area of 1 cm^2 be used in the exposure assessment thus leading to a reduction in the estimated exposure of 1/40 because of incomplete skin contact. It was stressed at this meeting that proper use of the product would not lead to any contact of the tape with the skin at all because the tape system is at the outside of the product (the side not making contact with the skin). The assumption of a limited contact area of 1 cm^2 - the actual figure in itself is an arbirtrary choice - is meant to take into consideration any inadvertent/infrequent contact of tape with the skin. Using the correction factor of 1/40 leads to estimated systemic exposure levels of 0.7 micrograms DOT/kg body weight/day (for napkins) and 0.3 micrograms TPT/kg body weight/day 0.35 micrograms DBT/kg body weight/day (for pilches).

A further correction factor may be applied for the incomplete dermal penetration (barrier function of the skin). As given in Appendix 4 for triphenyltins the factor of 1.3 is applicable. Thus, the systemic exposure for TPT is estimated at 0.23 micrograms TPT/kg body weight/day for pilches. For dibutyltins and dioctyltins such a factor is not available (no percentages for dermal and oral absorption are known).

[12] According to industry (information provided at the meeting of September 11, 1998) what was present in the napkins was *in*organic tin instead of organic tin (thus, the validity of chemical analysis carried out by Alberts and Dannen was questioned). We have contacted Dr. Bragt again on this issue. According to information provided by Dr. Dannen the original samples did contain organotins; this was confirmed by another test laboratory (Personal communication by Dr. Bragt, December 10, 1998). During the final meeting with industry on September 14, 1999 it was agreed by all parties that the original chemical analyses had been correct.

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Appendix 2 Selected toxicity data on dialkyltins

INTRODUCTION

The dermal and oral routes are of importance for the current problem. Both local and systemic effects may occur. In particular, effects on the skin/mucous membranes (irritation and sensitization) appear important because intensive contact with the skin or mucous membranes may be expected to occur with several of the items sampled (sanitary towels, tampons, napkins). The degree of the systemic exposure is determined by the dermal and oral absorption. For this reason in the brief review presented below the data on what is known with regard to the degree of absorption have been included.

TOXICITY DATA ON DIALKYLTINS (DIBUTYLTINS & DIOCTYLTINS)

The amounts of toxicological data, available for the dialkyltins (dibutyl and dioctyl) are relatively limited. Several oral subacute studies are available for this group focusing specifically on immunotoxicological effects; these studies have nearly all been conducted in rats using dibutyltin chloride or dioctyltin chloride as test substance. Limited data are available for the dioctyl compounds with regard to chronic toxicity, genotoxicity and carcinogenicity.

The toxicology of the dialkyltins is summarized by WHO/IPCS (IPCS, 1980), in the report by Hunt and Wilkinson (1990) (which was the basis of the summary presented in the monograph of the WHO *Guidelines for Drinking-Water Quality,* 1992/1996), in the ATSDR report (1992) and in the RIVM Scoping-document (1993). Dioctyltin compounds have been assessed by the Working Group on Food Contact Materials of the Scientific Committee Food of the EU (for the purpose of use as heat stabilizer in PVC). This assessment was based on the data summarized by the RIVM in 1989 (RIVM, 1989). On behalf of the EU, RIVM recently carried out a re-evaluation of the dioctyltin compounds (RIVM, 1999). The latter evaluation is yet to be submitted to the EU Working Group.

Data with regard to the dermal and oral absorption are lacking. For the dialkyltins, only usable data on oral toxicity are available (no dermal toxicity studies). These are summarized in Hunt and Wilkinson (1990) and in RIVM (1989, 1999). These data show that the most important target organ for the dialkyltins is the immune system with suppression of the thymus-dependent immune functions as effect. This was demonstrated for dibutyltin chloride and dioctyltin chloride in various studies of short duration in rats. With dose levels ≥50 ppm in the feed (administration period 2 to 6 weeks), a decrease of the thymus weight and a lymphocyte depletion in the thymus and thymus-dependent parts of the spleen were observed

(study conducted by Seinen and Willems, 1976 and Seinen et al., 1977b). From these experiments a NOAEL cannot be derived (LOAEL 50 ppm in the feed, corresponding with approximately 2.5 mg/kg body weight/day). In RIVM (1989), other studies of short duration are mentioned, conducted with dioctyltin chloride in young rats. The lowest effect level (LOAEL) found in these experiments is 1.25 mg/kg body weight/day (no NOAEL derivation possible). In two other subacute oral studies in rats (results summarized by Hunt & Wilkinson, 1990) effects on the bile ducts (150 ppm dibutyltin chloride in the feed, study by Seinen et al., 1977a) and neurotoxicity (20-80 mg dibutyltin laurate/kg body weight, study by Alam et al., 1988) was observed. No NOAEL is derivable from these studies either. Effects on the liver were seen in rabbits after administration of dibutyltin chloride (4-20 mg/kg body weight/day) and dibutyltin laurate (15-40 mg/kg body weight/day) during a period of 6 weeks (study by Tanaka et al. 1980). These experiments do not allow derivation of a NOAEL.

In RIVM (1989), the result of a chronic oral experiment in rats (unpublished data) is summarized. In this study, a mixture of octyltin chloride and dioctyltin chloride was tested in the feed (test concentrations 0, 4.95, 14.5, 45.5 and 115.4 mg/kg feed) during a period of 24 months. In this experiment an increased leucocyte count (two highest dose levels) thymus weight changes (two highest dose levels) and malignant lymphomas (two highest dose levels) were seen. The NOAEL derived from this experiment is 14.5 mg/kg feed (0.72 mg/kg body weight/day) (RIVM, 1989).

The available genotoxicity data for dialkyltins are in part contradictory, as shown by the summaries provided by Hunt & Wilkinson (1990) and RIVM (1989) of the studies that were carried out. With the Ames-test a positive result for dioctyltins was found by various research workers in one of the test strains used, in the absence of metabolic activation; however, in some other studies (same test strains), this result was not found. With mutation tests in mammalian cells *in vitro,* a positive result was reported for dibutyltin chloride and dioctyltin chloride in some studies. Other tests for this endpoint, however, were negative. A mixture of organotins (main component dioctyltin-bis(2-ethyl-hexyl-thioglycolate)) was negative in a test in yeast cells and in the micronucleus test in mice *in vivo* (these last two tests are unpublished data submitted by industry). On the basis of the test results presented in the RIVM (1989), the conclusion was drawn by the Working Group on Food Contact Materials of the Scientific Committee Food of the EEC in 1989 that dioctyltin chloride (no other dialkyltins were assessed by this working group) is probably not genotoxic.

The available carcinogenicity data are summarized by Hunt & Wilkinson (1990) and in RIVM (1989). In an NCI study from 1979, dibutyltin acetate was tested orally in rats and mice. The result did not indicate a carcinogenic effect. In the two-year study in rats mentioned above (unpublished study submitted by industry), with use of a mixture of octyltin chloride and dioctyltin chloride, a slight rise of the incidences of thymus tumours (highest dose level) and malignant lymphomas (two highest dose levels) was reported (RIVM, 1989).

In the most recent toxicity evaluation by the RIVM (RIVM, 1999) a two generation study in rats is presented. In this study a mixture of dioctyltin and monooctyltin was tested. The NOAEL in this study was 1.9 mg/kg bw/day (mixture), a dose level that corresponds with 1.5 mg/kg bw/day dioctyltin. Oral teratogencity studies in rats and rabbits were carried out with the same mixture. The NOAEL in rats was 5 mg/kg bw/day (expressed as the mixture) and in rabbits this was 1 mg/kg bw/day (expressed as the mixture; LOAEL 10 mg/kg bw/day) (RIVM, 1999).

The toxicological data for dioctyltins have been used by the Working Group on Food Contact Materials of the Scientific Committee Food of the EEC to derive a toxicological limit value (TDI) for dioctyltin compounds. This was done in the past in 1989. Since a new evaluation by RIVM is now available (to be submitted to the EU Working Group in the near future) this can now be used in the present report. In RIVM (1999) the NOAEL of 0.72 mg/kg body weight/day derived from the chronic rat experiment (test mentioned above) is used to derive a TDI for the entire group of dioctyltin compounds of 0.6 microgram/kg body weight (expressed on a tin basis). Expressed as dioctyltins, the TDI corresponds with 2.3 microgrammes/kg body weight.

CONCLUSIONS

From the toxicological data available for the dialkyltins the following conclusions are drawn:

- there are no data available with regard to the degree of absorption (dermal, oral) of the dialkyltins;
- the induction of immunotoxicological effects (suppression of thymus-dependent functions) by dialkyltins after oral administration has been demonstrated unequivocally;
- the NOAEL of 0.72 mg/kg body weight/day derived from a 2-year study in rats (dioctyltin) may be considered a preliminary NOAEL for the immunotoxic effect of the dialkyltins;
- no usable data with regard to the skin effects of the dialkyltins after dermal contact were found in the consulted toxicity reviews;
- the TDI of 2.3 μg/kg body weight (derived for dioctyltin compounds) can be used for an initial risk assessment of oral/systemic exposure to the dialkyltins.

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Appendix 3 Selected toxicity data on trialkyltins

INTRODUCTION

For tributyltin compounds a relatively large data set is available, consisting mainly of research conducted with tributyltin oxide (TBTO). There are hardly any data on the trioctyltin compounds. Below the toxicological information that is relevant for the present problem is briefly summarized.

TOXICITY DATA ON TRIALKYLTINS (TRIBUTYLTINS & TRIOCTYLTINS)

The toxicology of the trialkyltins has been reviewed by WHO/IPCS (IPCS, 1980), in the report by Hunt and Wilkinson published in 1990 (which was the basis of the summary presented in the monograph of the WHO *Guidelines for Drinking-Water Quality,* 1992/1996), in the ATSDR report (1992) and in the RIVM Scoping-document (1993). The WHO/IPCS published a EHC in 1990 on tributyltins (IPCS, 1990). Tributyltin oxide (TBTO) has been evaluated by the RIVM in 1993/1994 for the project 'Bodeminterventiewaarden' (RIVM, 1995). Recently, the US-EPA published a new assessment for TBTO (US-EPA, 1997).

As already mentioned, no toxicological data are available for trioctyltin compounds (conclusion based on the toxicity reviews that were consulted). For the tributyltins many data are available; this involves virtually exclusively studies performed with tributyltin oxide. This substance has been studied in many toxicological studies. These are nearly all oral studies. The consulted literature only mentions one dermal toxicity study of limited scope. The few data available for other tributyltins (than TBTO) suggest that these possess toxicological properties comparable to TBTO (conclusion based on the toxicity reviews that were used).

Dermal absorption of TBTO occurs with skin contact. In IPCS (1990), a dermal absorption percentage of 10 to 15% is given (derived from a study in monkeys). The same source gives absorption percentages of 25 to 50% for the oral route (BUA, 1988; IPCS, 1990). Research in rats showed that TBTO is transported through the blood-brain barrier and that the substance also crosses the placenta (IPCS, 1990).

In experimental animals, TBTO produces irritation of the eyes and skin. These effects were observed at ≥0.5% (skin) and 0.15% (eyes); no level-without-effects (NOAEL) is derivable for these endpoints. In human beings, TBTO may cause severe dermatitis after direct skin contact (conclusion based on *case studies*). This reaction has a delayed character, i.e. the symptoms develop no sooner than some hours after the start of contact. The dose-effect relation for this effect is unknown. The lowest effect concentration reported is 0.01 g/litre

(value derived from a *case study*); the concentration at which this effect is no longer seen is unknown (IPCS, 1990; BUA, 1988; RIVM, 1995). The observed dermatitis is probably not a hypersensitivity response. No effect was seen in a standard test for dermal sensitization in guinea pigs, which is the only study available for this endpoint (IPCS, 1990).

Several oral toxicity experiments of short duration have been performed with TBTO. For the greater part, these experiments were performed by the RIVM. In addition, a chronic experiment in rats has been performed, also by the RIVM. The main target organ for TBTO is the immune system. This substance induces suppression of the thymus-dependent immune functions. Evidence has been found indicating a causative role of the dibutyltin metabolite with regard to this effect. In the 2-year study in rats for TBTO, concentrations of 0.5 and 50 mg TBTO/kg feed were tested. The main effects seen were: histological changes in the kidneys, the liver and the bile ducts, changes in immune globulin concentrations and lymphocyte count in the blood, and suppression of resistance for the nematode *Trichinella spiralis*. The NOAEL derived from this experiment was 0.5 mg/kg feed (0.025 mg/kg body weight/day) (WHO-WQG, 1992/1996; US-EPA, 1997).

The genotoxicity of TBTO has been evaluated in a large number of test systems. The results of nearly all of these studies did not indicate any effect. The conclusion is therefore that TBTO is not genotoxic (IPCS, 1990; US-EPA, 1997).

The carcinogenicity of TBTO has been studied in two oral animal studies in rats and mice, respectively. The importance of the increased incidences of some tumour types (pituitary gland, adrenal, parathyroid) in rats with use of the highest dose level is not clear (the incidences found are within the very variable historical control ranges). No effects were found in the study in mice (study conducted by Daly, 1992). On the basis of these results the conclusion is drawn that insufficient evidence exists for a carcinogenic effect of the substance (IPCS, 1990; RIVM, 1995; US-EPA, 1997).

Various oral teratogenicity studies with TBTO have been conducted in rats, mice and rabbits. The results of these studies provided evidence of teratogenic effects (cleft palate) in mice and rats with dose levels which were toxic for the mother animals (≥11.7 mg/kg body weight/day). The lowest NOAEL in these studies was 1 mg/kg body weight/day (IPCS, 1990). The reproduction toxicity of TBTO was studied in an oral two-generation experiment in rats (study by Schroeder, 1990). In this study, the critical toxic effect in the parent animals was thymus weight reduction (LOAEL 2.95 mg/kg body weight/day; NOAEL 0.29 mg/kg body weight/day). No effect on the reproduction parameters was seen. The only effect observed in the offspring was a diminished pup weight during the lactation period (LOAEL 3.43 mg/kg body weight/day; NOAEL 0.34 mg/kg body weight/day) (US-EPA, 1997).

Hardly any toxicity data are available for the dermal route. The only study found in the literature was a study performed in mice in 1984. Effects on the kidney were found after dermal administration of 10 and 40 mg TBTO/kg body weight/day (solvent not mentioned) (ATSDR, 1992).

The toxicological data on TBTO have been used to derive toxicological limit values. For the oral route the WHO-WQG determined a TDI (chronic limit value) in 1992 of 0.25 micrograms/kg body weight on the basis of the NOAEL OF 0.025 mg/kg body weight from the chronic rat experiment.

CONCLUSIONS

From the toxicological data available for the trialkyltins the following conclusions are drawn:
- of the substances in this group, TBTO is the one which has been studied most extensively; no data are available for trioctyltins;
- the limited data available for other tributyltins indicate an effect comparable to that of TBTO;
- TBTO is absorbed by the skin (absorption percentage 10 to 15%)
- for TBTO absorption percentages of 25 to 50% are given for the oral route;
- TBTO is strongly irritating for the skin; a NOAEL (concentration or dose level without effect) for this is lacking (lowest known effect level: 10 mg/litre);
- limited data indicate that TBTO does not have a sensitizing effect on the skin;
- the performed experiments do not indicate any genotoxicity or carcinogenicity by TBTO;
- data from a large number of oral toxicity studies show that TBTO has an immunotoxic effect (suppression of thymus-dependent immune functions); the chronic NOAEL for this is 0.025 mg/kg body weight/day;
- the TDI of 0.25 μg/kg body weight (derived for TBTO) can be used for an initial assessment of risk following oral/systemic exposure to the trialkyltins.

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Appendix 4 Selected toxicity data on triphenyltins

INTRODUCTION

A great deal of oral standard experimental animal research (data developed by industry for the purpose of authorization as a pesticide) has been conducted with the triphenyltin compounds (chloride, hydroxide, acetate). Below the information that is relevant for the present problem is summarized.

TOXICITY DATA FOR TRIPHENYTLTINS

The triphenyltins, often referred to in short as *fentin*, are used as fungicides. The following compounds are of importance here: triphenyltin acetate, triphenyltin chloride and triphenyltin hydroxide. Many toxicity experiments have been performed with fentin (standard experimental animal studies for pesticide registration purposes). The toxicology of fentin is has been evaluated by the WHO/FAO in 1991 (JMPR, 1992). In addition to a large number of oral studies, dermal studies have been performed to assess irritation, sensitization and systemic toxicity.

During dermal contact, fentin is absorbed relatively easy by the skin. In rat experiments up to 55% of the dose was absorbed after dermal application, with 30% of this amount reaching the blood stream and up to approximately 20% remaining in the skin (local binding) (JPMR, 1992; RIVM, 1993).

In a few experimental animal studies with fentin (acetate and hydroxide tested), no or very little dermal irritation was seen with very high concentrations. With undiluted fentin an severe eye irritation was observed (the NOAEL for this effect is unknown). In sensitization studies in guinea pigs, the hydroxide did not have a sensitizing effect, but the acetate did. The dose-response relation for this sensitizing action is unknown (no NOAEL known for induction of hypersensitivity or for response stimulation in sensitized individuals).

In oral studies of short and long duration, an immunosuppressive effect of fentin was observed. The NOAEL for this in mice was 5 mg/kg feed (1 mg/kg body weight/day) based on a thymus weight reduction with 25 mg/kg feed. In rats, the NOAEL for effects in the immune system was 25 mg/kg feed (1.7 mg/kg body weight/day) based on reductions of immunoglobulin G and leucocyte and lymphocyte count in the blood with 50 mg/kg feed. In chronic experiments in rats, an effect (an increased mortality rate and a reduced immunoglobulin level in the blood) was seen even with use of the lowest level tested, i.e. 5

mg/kg feed (0.3 mg/kg body weight/day). This level is therefore considered as the overall-LOAEL derived from these experiments (a NOAEL cannot be derived) (JMPR, 1992).

Many genotoxicity experiments have been performed with fentin. The results led to the conclusion by the JMPR (1992) that no genotoxic hazard for humans is involved with use of fentin (an effect was observed in a few of the *in vitro* experiments performed, but the available *in vivo* tests proved negative, indicating that the inherent potency encountered *in vitro* does not become manifest *in vivo*).

The carcinogenicity of fentin was evaluated in oral studies in rats and mice. Increased incidences of liver tumours were found in mice. In rats, the incidences of pituitary gland tumours and testis tumours was increased; these tumours were accompanied by non-neoplastic changes in these organs. The non-neoplastic changes in the pituitary gland were also present with lower dose levels which did not induce tumours (JMPR, 1992). No further statements are made in the JMPR's evaluation concerning the interpretation of the observed tumours (relevance for humans). Judging by the final conclusion made by the JMPR, they are apparently not considered relevant.[13]

Embryotoxicity and maternal toxicity were found in teratogenicity studies in rats, hamsters and rabbits. Fentin did not produce a teratogenic effect in these studies. The rabbit was the most sensitive species with a NOAEL for embryotoxicity of 0.3 mg/kg body weight/day and a NOAEL for maternal toxicity of 0.1 mg/kg body weight/day. The reproduction toxicity was studied in a two-generation experiment in rats. The NOAEL in this experiment was 5 mg/kg feed (0.4 mg/kg body weight/day) with reduced litter size, reduced pup weight and reduced weight of the spleen and the thymus in the offspring as critical effects (JMPR, 1992).

Two toxicity experiments were performed in rats with dosing via the dermal route, which are both summarized in JMPR (1992). In one of these studies (test period 3 weeks) only skin irritation was seen (no systemic effects). The administered concentrations of the substance are not mentioned in the monograph made by the JMPR, therefore no information can be obtained from this experiment with regard to the dose-response relation for the occurrence of skin irritation with repeated dermal exposure. The same applies to the other dermal experiment (administered concentrations not mentioned). Contrary to the other experiment however, systemic effects were seen in this experiment (including a reduction of the lymphocyte count in the blood). The NOAEL in this experiment was 10 mg/kg body weight/day (JMPR, 1992).

[13] The final conclusion of the JMPR Working Group was that an ADI was derivable, which implies that the Working Group does not consider the substance to be a carcinogen with a genotoxic action. The conclusion drawn by the Working Group (based on the available genotoxicity study) that the use of fentin does not involve any genotoxic risk for humans is consistent with this.

In 1991, JMPR proposed a chronic oral limit value (ADI) for fentin of 0.5 micrograms/kg body weight/day based on a chronic LOAEL of 0.3 mg/kg body weight/day (JMPR, 1992).[14]

CONCLUSIONS

From the toxicological data available for the triphenyltins the following conclusions are drawn:

- triphenyltins are absorbed by the skin (absorption percentage 55%; 30% reaches the systemic circulation);
- the average absorption percentage for the oral route is 40%;
- the available data indicate that triphenyltins have no or hardly any irritating effect on the skin (even with very high concentrations, there is no effect or only a weak effect);
- triphenyltins may have a sensitizing effect on the skin (conflicting results); the dose response relation for this potential effect is unknown;
- on the basis of the experiments performed, triphenyltins are not considered carcinogens acting through a genotoxic mechanism;
- triphenyltins are immunotoxic (suppression of thymus-dependent immune functions); the corresponding NOAEL is 1 mg/kg body weight/day in mice and 1.7 mg/kg body weight/day in rats;
- the ADI 0.5 μg/kg body weight is applicable for an initial risk assessment of oral/systemic exposure.

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[14] More precisely: the JMPR working group decided to maintain the ADI derived in 1970, because parts of the LOAEL of 0.3 mg/kg body weight/day led to a value comparable to the old ADI because of the presence of a safety factor 500.

Appendix 5 Mailing list

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