Committee for Risk Assessment

RAC

Annex 1 to the opinion on
new scientific evidence on the use of boric acid
and borates in photographic applications by
consumers

Background Document

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BACKGROUND DOCUMENT TO THE OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON NEW SCIENTIFIC EVIDENCE ON THE USE OF BORIC ACID AND BORATES IN PHOTOGRAPHIC APPLICATIONS BY CONSUMERS

1. INTRODUCTION

The element boron does not exist in nature by itself but it combines with oxygen and other elements to form boric acid, or inorganic salts which are generally referred to as "borates". Most of the simple inorganic borates exist predominantly as undissociated boric acid in dilute aqueous solution at physiological and environmental pH, leading to the conclusion that the main species in the body water of mammals and in the environment is undissociated boric acid. Boric acid is a Lewis acid (hydroxide ion acceptor) rather than a Brønsted acid (proton donator). The following equilibrium is found $B(OH)_3 + 2H_2O \leftrightarrow [B(OH)_4]^- + H_3O^+$; pKa = 9.0 at 25°C. Boric acid exists mainly as undissociated boric acid $B(OH)_3$ at pH < 5, whereas at pH > 12.5 the metaborate ion $[B(OH)_4]^-$ becomes the main species in solution. Both species respectively polynuclear complexes are present at pH 5 to 12.5.

As these substances are present inter alia as boric acid and as borate anion at environmentally and physicologically relevant concentrations in aqueous solution, the systemic effects and also some of the local effects of simple inorganic boron compounds can be traced back to boric acid. Results from one substance can be transferred to evaluate the other substance on the basis of boric oxide (B_2O_3) (hydrolysed boric oxide is present as boric acid in aqueous solution $B_2O_3 + 3\ H_2O \rightarrow B(OH)_3$) or by using boron equivalents, calculated by the fraction of boron on a molecular weight basis. Conversion factors are given in table 1 below.

Table 1: Conversion factors to Boron Equivalents

	CAS#	EC#	Substance	Conversion factor for Equivalent dose of B
Boric acid	10043-35-3	233-139-2	H_3BO_3	0.175
Boric acid, crude natural #	11113-50-1	234-343-4	Not specified	-
Diboron-trioxide, boric oxide	1303-86-2	215-125-8	B_2O_3	0.310
Disodium tetraborate decahydrate	1303-96-4	215-540-4	$Na_2B_4O_7 * 10H_2O$	0.113
Disodium tetraborate pentahydrate	12179-04-3	215-540-4	$Na_2B_4O_7 * 5H_2O$	0.148
Disodium tetraborate anhydrous *	1330-43-4	215-540-4	$Na_2B_4O_7$	0.215
Tetraboron disodium heptaoxide, hydrate *§	12267-73-1	235-541-3	$B_4Na_2O_7.x\ H_2O$	-
Orthoboric acid, sodium salt *§	13840-56-7	237-560-2	$BH_3O_3.x\ Na$	-

There is another entry on the fourth priority list[1] for boric acid, CAS# 11113-50-1, EC# 234-343-4, which is described as "crude natural, containing not more than 85% of H_3BO_3, calculated on a dry weight basis". This substance is a Low Production Volume substance[2]. Further, the according EINECs entry was changed in that the sentence "crude natural, containing not more than 85% of H_3BO_3 calculated by weight" has been deleted in 2002 (OJ of the EC 2008/C 54/08, March, 2002). The current EINECS index therefore contains two entries for boric acid, one being specified by the formula (CAS# 10043-35-3, EC# 233-139-2, boric acid, BH_3O_3) while the other entry remains unspecified (CAS# 11113-50-1, EC# 234-343-4, boric acid).

* substances summarised under index number 005-011-00-4, Annex VI (EC) No 1272/2008 (the "x" in the formula indicates an unspecified number of waters of crystallisation and sodium, respectively)

§ The opinion does not cover these substances because RAC has received specific indications from industry that they are no longer on the EU market

[1] Commission Regulation (EC) No 2364/2000 concerning the fourth list of priority substances as foreseen under Council Regulation No 793/93.
[2] ECB ESIS: European chemical Substances Information System, Version 5.00

Aqueous solutions of the pure substances boric acid and diboron-trioxide result in an acidic pH, whereas the other substances lead to an alkaline pH. Photographic developers (main application of boron for photochemicals) contain various substances and generally reveal an alkaline pH (8-9).

2. HUMAN HEALTH EFFECTS

2.1) Justification that effects on fertility and developmental effects are the leading health hazards of boron compounds

A detailed overview on toxicokinetics and human health effects can be found in Austria (2009). A summary is included in Annex IV.

2.1a) Foetal development is one main target of boron toxicity. Developmental effects comprise reduced foetal body weight as well as skeletal and visceral malformations in different species (rat, mouse and rabbit)

2.1b) Several repeated dose toxicity studies identified the testis as main target of boron toxicity (rat, mouse, deer mouse, dog). These effects were supported by fertility studies which found male as well as female fertility affected after boron administration. The most severe effects seen in repeated dose toxicity studies were effects on testes and spermiation. Hormone levels (FSH, LH and testosterone) were also changed. Cross over mating trials in rats and mice revealed infertility for treated males with untreated females and treated females with untreated males.

2.1c) For acute effects, respiratory and eye irritation were described after exposure to airborne boron compounds. Effects on eyes were only seen for disodium tetraborate pentahydrate and decahydrate (read across to disodium tetraborate anhydrous is possible), while boric acid induced only reversible effects which do not justify classification. In contrast, effects on the respiratory tract were described for disodium tetraborates and boric acid. From several studies on humans and one Alarie test in mice it can be derived that boron compounds are sensory irritants. In Austria (2009) a DNEL was derived based on a NOAEC of 0.8 mg B/ m^3. It was stated that the same value would also be protective with regard to eye irritating effects (for details see Austria (2009) & Annex IV). However, it was not discussed within the RAC whether sensory irritation or a DNEL derived for the occupational setting was relevant for the evaluation of risks resulting from the application of photochemicals by consumers.

2.2) Decision on the appropriate dose descriptors

2.2a) With regard to developmental effects no human data exist. The available data from animal studies are sufficient to conclude that prenatal exposure to boron by the oral route can cause developmental toxicity. Developmental effects were seen in three different mammalian species, namely rat, mouse and rabbit, with the rat being most sensitive. From the most robust study in rats (Price et al., 1996) the lowest NOAEL = 9.6 mg B/kg bw/day can be derived. Reduced foetal body weight per litter and increased incidence in short rib XIII were seen at the LOAEL = 13.3 mg B/kg bw/day. In another rat study a LOAEL = 13.7 mg B/kg bw/day for skeletal effects (short rib XIII) was derived (Heindel et al., 1992). Other effects seen at maternally toxic doses were visceral malformations like enlarged ventricles and cardiovascular effects.

2.2b) Fertility effects of boron compounds were investigated in several epidemiological studies in workers and populations living in areas with high environmental levels of boron. Truhaut et al., 1964, Tarasenko, 1973, Krasovskii et al., 1976, Whorton, 1994, Tuccar, 1998 and Sayli, 1998, 2001, 2003 were available at the time the Commission Working Group of Specialised Experts in the field of Reprotoxicity (Ispra, October 5-6, 2004) was held. They came to the conclusion that the epidemiological studies available at that time were of insufficient quality to demonstrate presence or absence of fertility effects. A recent review, on studies carried out on Chinese boron workers (Scialli et al., 2009) was generated by an expert panel initiated by industry. It allows no final conclusion on effects of boron exposure on human fertility.

Male infertility was observed in studies in rats, mice, deer mice and dogs (Weir, 1966a, b, c, d, Fail et al., 1991, Dixon et al., 1979, Lee et al., 1978, Treinen & Chapin, 1991, Fail et al., 1989). The underlying cause for male infertility was identified to be testicular atrophy. A series of studies was published providing insight into the mechanistic nature of the lesions in rats. Good correlation between doses inducing spermatogenic arrest and infertility could be observed. The effects were reversible at lower doses, but no recovery occurred at doses causing germ cell loss. Germinal depletion correlated well with increased plasma levels of FSH. Levels of other hormones, like testosterone and LH were not always affected. A NOAEL of 17.5 mg B/kg bw/day in rats (Weir, 1966a,b,c,d) could be derived.

Female fertility was affected as demonstrated by Fail et al. (1991) and Weir (1966c, d). The underlying mechanism is much less investigated than for effects on male fertility. Effects observed were infertility in female rats at 58.8mg B/kg bw/day (Weir, 1966c,d) and reduced fertility in female mice at 111.3mg B/kg bw/day (Fail et al. 1991).

Fail et al. (1991) investigated different endpoints at different dose levels in a continuous breeding study according to the NTP protocol. The following effects in female mice were seen at the lowest dose at which these effects were investigated (LOAELs). F0 females had normal cyclicity, but revealed reduced average dam weight on post natal day 0, reduced average gestational period and their litters showed significantly reduced weight when adjusted for litter size (111.3mg B/kg bw/day). The last observation was also seen in litters from the F1 generation. In contrast to F0 females the oestrus cycle length was reduced in F1 females (26.6mg B/kg bw/day).

Weir (1966c,d) described infertility of female rats at 58.8 mg B/kg bw/day when paired with untreated males (only 2 out of 16 matings produced litter). With regard to number of conceptions, number and size of litters, number of deaths, weight of pups at 24 hours and at weaning as well as cross signs of abnormalities no differences compared to control animals were recorded at 17.5 mg B/kg bw/day. A NOAEL of 17.5 mg B/kg bw/day could be derived.

2.3) Rationale of DNEL derivation - choice of assessment factors (AFs)

2.3 a) Interspecies differences

The studies used for DNEL derivation were carried out in rats. Animal studies suggest that interspecies variability in toxicodynamics exists. Absorption and distribution of boron compounds are similar in rats and humans, and boron is not metabolised. A 3 to 4 times faster elimination rate in rats compared to humans was described to be the major difference with regard to toxicokinetics.

Based on the described similarities between rats and humans the interspecies default assessment factor of 10 was reduced to 3.16 in the IPCS monograph on Boron (WHO, 1998). While the factor of 2.5 for toxicodynamics was not changed in this monograph the factor for allometric scaling was reduced from 4 to 1.26.

In two other WHO documents evaluating boron toxicity (WHO, 2003, 2009) as well as in EFSA (2004) the values for the interspecies default factor were not reduced. They referred to Dourson et al. (1998), who evaluated the available toxicokinetic data and concluded that additional studies were needed on rats to be able to modify the interspecies assessment factors with confidence.

In the Biocides Report (2009) the standard assessment factor of 10 for interspecies variation was not reduced.

With regard to toxicokinetic differences between rat and human the RAC concluded that the available data are not sufficient to reduce the factor for allometric scaling. No deviation from the default assessment factor of 10 for extrapolation from rat to human was introduced.

2.3 b) Intraspecies differences

Intraspecies variation of boron toxicokinetics relates primarily to variations in clearance. Half-life values in volunteers administered boric acid orally and intravenously were the same by either route and had a duration of approximately 24h or less (Jansen et al 1984, Schou et al 1984). The average half-life value from case reports in almost 800 patients poisoned with boric acid was 13.4h, ranging from 4-27h (Litowitz et al 1988). Incomplete or inconsistent patient histories contribute to the variation of the measured half-life values.

In the IPCS monograph from 1998 the intraspecies assessment factor was reduced from 10 to 8. Human data suggest some limited variability in boron absorption and distribution. However, due to the lack of boron metabolism in humans and experimental animals the default value for kinetic differences was reduced from 3.16 to 2.5. It was concluded that the available data on toxicodynamics did not support a deviation from the default of 3.16.

The background document for development of WHO Guidelines for Drinking Water Quality (WHO 2003, 2009) and EFSA (2004) have proposed an uncertainty factor of 6 instead of 10 for intraspecies variation. The basis for this modification relies on an assessment of the glomerular filtration rate (GFR) and its variability in pregnant women (Doursen et al. 1998), the vulnerable group with regard to effects on the developing foetus. In the absence of data describing clearance of boron in pregnant women, the mean GFR in 36 healthy women (144 ± 23 ml/min in early pregnancy and 145 ± 32 ml/min in late pregnancy) was used as surrogate. In order to estimate the degree of intraspecies variation, the ratio of the mean GFR (144ml/min) during late pregnancy and the mean GFR minus two standard deviations (i.e. 144 – (2 x 32) = 80) was calculated. This results in a value of 1.8 for the toxicokinetic component of the intraspecies assessment factor, and an overall factor of 6, rounded from 5.7.

It has to be noted that Dourson et al. (1998) only included healthy pregnant women in their evaluation and data from different studies were pooled. It is possible that in these studies different methods were used to assess GFR which would have a strong impact on the results. The value of 1.8 only considers the lower range of the GFR variability among healthy pregnant women.

In the Biocides Report (2009) the standard assessment factor of 10 for intraspecies variation was not reduced.

Due to the urgency of the current request to RAC the time to evaluate the data with regard to their suitability to reduce the intraspecies assessment factor was not sufficient. For the present evaluation the default of 10 is used for DNEL derivation.

2.3 c) Quality of the whole database and exposure duration

No additional factor is needed as the overall database includes sub-chronic and chronic studies on several species and several studies on reproductive toxicity. These studies cover the relevant exposure durations for the effects evaluated and are relevant for the exposure scenarios under assessment.

2.3 d) The DNEL for developmental effects is the leading DNEL

$NOAEL_{developmental\ effects}$ = 9.6 mg B/kg bw/day (Price et al., 1996)	AF = 100 (interspecies – rat to human: 10; intraspecies: 10)	$DNEL_{systemic}$ = 0.096 mg B/kg bw/day
$NOAEL_{effects\ on\ male\ \&\ female\ fertility}$ = 17,5mg B/kg bw/day	AF = 100 (interspecies – rat to human: 10; intraspecies: 10)	$DNEL_{systemic}$ = 0.175 mg B/kg bw/day

2.4) Dermal absorption

Several studies report that dermal absorption of boron compounds across intact skin is low in human new-born infants (no rise in plasma boron levels; Friis-Hansen et al., 1982), adult humans (no increase in boron excretion in urine; Beyer et al., 1983; Hui et al, 1996; Wester et al, 1998), rabbits (Draize and Kelley, 1959), and rats (no or slight increases in urine boron concentration

Nielsen, 1970). In contrast, borates have been demonstrated to penetrate damaged or abraded skin (Draize and Kelley, 1959; Nielsen, 1970, Stüttgen et al., 1982). The use of different vehicles may change the absorption through diseased skin (Nielsen, 1970 and Stüttgen et al, 1982).

It is well known that boron compounds absorbed by the organism rapidly lead to a rise in urine boron concentrations (Nielsen, 1970, Jansen et al. 1984, Sutherland et al. 1998). Most of the above listed studies had, however, difficulties when analysing minimal rises in urine boron content after dermal absorption. These analytical difficulties are aggravated by the fact that natural urine boron concentrations are prone to changes depending on dietary composition.

Wester et al. (1998) tried to overcome these analytical difficulties. They applied ^{10}B-enriched boron compounds in two separate studies, one in vivo study involving human volunteers and one in vitro study using human cadaver skin. The applied boron compounds contained 99% ^{10}B, while the natural distribution is 19% ^{10}B to 81% ^{11}B.

Skin absorption data were obtained in human volunteers (Wester et al., 1998). They were advised to avoid boron rich food or other boron sources and to keep a feed diary. The volunteers (8 per group) were dosed (non-occluded) with boric acid or disodium tetraborate decahydrate (borax; 5% in aqueous solution). A volume of 1.8ml was spread over an area of 900cm^2 (30cm x 30cm) on the volunteer's backs which resulted in a dose of 2µl/cm^2, which was stated to be the maximum volume not running off the skin. The delivered dose was quantified by weighing the syringe before and after dosing. The dosed area was allowed to air dry and then the volunteers were dressed in commercial T-shirts. Twenty-four hours later the residual dose was removed by washing. T-shirts and skin washes as well as urine samples were analysed for their boron content using coupled mass spectrometry.

To determine background ^{10}B to ^{11}B ratios and total boron content for the urine of each volunteer, pre-treatment urine was collected on 4 consecutive days (24 hour samples, day 1 to day 4). These data were used to calculate a baseratio for each volunteer.

On day 5 the first dose was applied to the volunteer's backs for 24 hours. From day 5 to day 11 post-treatment urine samples were collected (24 hour samples). On day 11 a 2% SLS (sodium lauryl sulphate) solution was spread over the volunteer's backs, followed by a second 24 hour application of boron test material on day 12. This treatment was intended to simulate absorption via irritated skin, however, it failed to induce skin irritation. No visible signs of irritation were noted and no difference in TEWL (transepidermal water loss) was measured before and after SLS-treatment. Continuous 24 hour urine samples were collected until day 17.

The ^{10}B concentrations in urine exceeding the pre-treatment values were regarded as the amount of boron absorbed via skin and were expressed as percent from the applied dose (table 2). The formulas used for calculating the excess ^{10}B excreted are presented in Annex II.

One of the main drawbacks of this study is that total recovery of the applied dose ranged from 48.8 - 63.6%, therefore 36.4-51.2% of the applied dose is not accounted for. The authors suggest that this may be due to loss to outside clothing and bedding. However, in this case the results would not reflect absorption over 24 hours but over the time until loss to outside clothing was made possible. Moreover, part of the lost dose may also be located in the body or in the skin at the application site, which hence should be considered as being absorbed.

From the original study report which was available to the rapporteur it can be derived that the ^{10}B concentrations in the pre-treatment urine samples as well as in the post-treatment samples exerted considerable variability. (This information is based on the calculated values, as the measured data for ^{10}B and ^{11}B content of the urine samples were not included in the study report.) As the urine boron concentration measured during the 4 pre-treatment days was used to set the baseline for the whole experiment the high variability of these values has a strong impact on the results of the whole study.

It was noted that boron excreted on day 11 (i.e. 6 days after the first application of test material) was not added to the amount excreted after the first treatment, although the values for day 11 were presented in the original study report. Moreover, it was recognised that for some individuals comparatively high ^{10}B concentrations were detected at the last sampling day (day 17). As this information can be extracted from the original study report percent absorption were also calculated including day 11 (in relation to the first dose applied) and for the total excreted amount of ^{10}B from day 5 to day 17 (in relation to the first + second dose applied), see table 2. As the application of 2% SLS-solution prior to the second application of boron compounds failed to induce skin irritation, also the second dose step can be regarded as an experiment on intact skin.

Table 2: Dermal Absorption in Humans of boric acid and disodium tetraborate decahydrate

	Boric acid (5%)		**Borax (5%)**	
	% absorbed ± SD	**Mean + SD**	**% absorbed ± SD**	**Mean + SD**
Days 5 to 10	0.226 ± 0.125	0.351	0.210 ± 0.194	0.404
Days 5 to 11 *	0.250 ± 0.118	0.368	0.225± 0.221	0.446
Days 12 to 17	0.239 ± 0.147	0.413	0.184 ± 0.219	0.403
Days 5 to 17 *	0.245 ± 0.133	0.378	0.205 ± 0.193	0.398

It further has to be criticised that the study assumed that 100% of boron absorbed via skin was excreted and that no accumulation occurred. The study is also flawed by lack of information about the volunteers regarding sex and race.

In a second experiment published by Wester et al. (1998) in vitro percutaneous absorption of ^{10}B enriched boric acid and disodium tetraborate decahydrate was tested on human cadaver skin in a flow through cell system. Absorption was determined by receptor fluid accumulation over a 24h dosing period and by skin content at the end of the 24h period. Receptor fluid was sampled every 4 hours. Most of the dose could be recovered.

1000µl of solutions of 5%, 0.5% and 0.05% boric acid and of 5% disodium tetraborate decahydrate (borax) were applied per cm^2 skin, which can be regarded as an infinite dose experiment. Wester et al. (1998) derived percent absorption, fluxes and Kp values. They applied statistical methods (Hoaglin et al. 1983) using the statistical analysis system SAS 6.1 (Cary, NC) in order to identify outliers. For identified outliers new values were imputed using least squares estimation from a linear model (Little & Rubin, 1987). These calculations were, however, neither presented in the original study report nor in the published paper and could therefore not be evaluated. The present evaluation therefore relies on recalculated Kp and flux values based on measured data from the original study report (see table 3). These values were used for scenarios with continuous direct contact to photochemicals, as dermal absorption from liquids is better described by the use of fluxes (Permeability (Kp) x concentration (C)) than by using percent absorption. This is supported by Moody & Chou (1995), Schneider et al. (1999), ICPS (2006) and US EPA (2004a, 2007).

Table 3: Fluxes and Kp-values calculated from an infinite in vitro experiment by Wester et al. (1998), at the 4-hour time point

Concentration of dosing solution	Flux (µg/cm^2/h)	Kp (cm/h)
5% Boric acid, 8165 µg $^{10}B/cm^3$	1.819	2.2×10^{-4}
0.5% Boric acid, 816.5 µg $^{10}B/cm^3$	0.039	4.8×10^{-5}
0.05% Boric acid, 81.6 µg $^{10}B/cm^3$	0.388	4.8×10^{-4}
5% Borax, 5270 µg $^{10}B/cm^3$	0.224	4.2×10^{-5}
Mean value of all Kp values		2×10^{-4}

Penetration increased over 24 hours, as the skin became more permeable during the prolonged wet conditions (see Figure in Annex III). Exposure durations of the scenarios of the present evaluation do not exceed 4 hours. Therefore the amount of ^{10}B detected in the receptor fluid after 4 hours was used instead of the 24 hours time point, in order to avoid an overestimation of skin absorption in these scenarios. For other risk assessments dealing with scenarios with longer exposure durations appropriate time points should be chosen for Kp derivation.

These values are derived from experiments using five different human cadaver skins. In contrast to the published study we excluded one skin (skin #4) for the recalculation of the results, as its integrity appeared to be affected (very high variability among different test units was observed). Integrity of the skins was not tested in the experiment. For the present evaluation the values were not corrected for outliers.

Fluxes, J (µg/cm^2/h), are supposed to increase with concentrations of the test substance in the donor liquid. This is not reflected by the values presented in table 3. In contrast to fluxes, Kp values (= Flux (J) divided by concentration in the donor liquid (C)) are substance specific values and should by definition be constant for a given substance across different concentrations. In our calculation there is a slight variability among the Kp values calculated for the different boron concentrations. The variability of the calculated fluxes and Kp values might be caused by considerable and differing amounts of test material retained within the skin during the experiment and by outliers which were not corrected for the present evaluation. The skin from the same donors were used to derive Kp values for solutions with different boron content. The highest Kp value (for the experiment testing 0.05% boric acid, see table 3) is therefore not demonstrating a rather permeable (sensitive) skin, but is rather caused by methodological variations. The mean value of all four Kp values is therefore the most appropriate value to describe dermal absorption from liquids for the present evaluation (see table 3).
As recommended in the OECD guidance document on dermal absorption (OECD, 2004) the test material contained within the skin was not included in the calculation of the Kp value, although considerable amounts of ^{10}B were detected within the skins when analysed at the end of the experiment. The amount detected within the skin ranged between 30% and 70% of the absorbed dose (absorbed dose = amount of ^{10}B detected in the receptor fluid + amount ^{10}B within the skin - the amount of ^{10}B washed from the skin surface after the experiment). The performance of a new in vitro study might therefore be considered for future evaluations.

Though predating GLP and OECD guidelines for skin absorption tests the in vivo rat skin absorption study by Nielsen (1970) appears to be well conducted and the data presented are judged useful for a weight-of-evidence approach. The study was designed to compare dermal boric acid absorption from aqueous versus oleaginous preparations, through intact and severely damaged skin. Compared to human studies the boron uptake via food can be considered to be more constant in experimental animals. Still, some variations in food consumption and boron content of the food could have occurred. In contrast to severely damaged skin for which absorption values were as high as 24% and 33% from the aqueous preparation, absorption via intact skin did not exceed 1.04%. Elimination half-life of boron in rats was estimated to be <13 hours (Farr and Konikowski, 1963; Ku et al. 1991; 1993) and as low as 3 hours by Vaziri et al. (2001). Therefore the tested time intervals seem relevant for evaluating dermal absorption. The aqueous jelly based preparation appears to demonstrate a relevant scenario for skin absorption from aqueous solutions. However, as the compound was applied in an aqueous jelly based vehicle the results cannot be compared directly to absorption from aqueous solutions of boron compounds. Furthermore, the amount of boron applied per cm^2 skin in the in vivo study by Wester et al. (1998) was 8.75 µg B, whereas Nielsen (1970) applied 310 µg B. This might have influenced the percentage of absorption.

As human in vivo studies are most relevant for human risk assessment and urinary boron was demonstrated to be a sensitive indicator for boron intake (Sutherland et al. 1998) the human in vivo data by Wester et al. (1998) were used to estimate dermal absorption. Though this study has several shortcomings the results are supported by toxicokinetic studies which indicate that boron

compounds have a low potential to accumulate in the body (for more information on toxicokinetics see Austria, 2009). Also the in vivo rat skin absorption study by Nielsen (1970) supports the low skin absorption values derived by Wester et al. (1998). Though it is not fulfilling modern quality requirements it supports low dermal absorption values through intact rat skin. Absorption values through intact rat skin did not exceed 1.04%. Several reports and guidance documents state that rat skin is typically two to ten times more permeable than human skin (ECETOC, 1993; Ross et al., 2000; Raavenzway et al., 2004), while other data support that rat skin permeability occasionally resembles human skin permeability (Ross et al., 2000).

In the Biocides Report (2009) as well as in Austria (2009) the in vivo study by Wester et al. (1998) was used to assess dermal absorption. The absorbed dose (in %) for boric acid, which was higher than for disodium tetraborate decahydrate, was used to derive a dermal absorption for boron compounds of 0.5% (rounded from 0.4%), following addition of the standard deviation (SD). The standard deviation was added to cover parts of the uncertainty resulting from the described shortcomings of the study. This value, which results from an observation period of the volunteers for 5 days after dermal administration of test material, is also used for the present evaluation in scenarios A1, A2, B1, B2, C1, C2, D1 and D2 covering exposure to dry powder or dried liquids.

From the infinite dose in vitro study by Wester et al. (1998) a Kp of 2.0 x 10^{-4} cm/h could be derived. This is the mean of four Kp values derived for solutions with different boron concentrations, at the 4-hour time point. As this value was derived based on the original data from the study report without correction for outliers the RAC recommends a reevaluation of this study for future assessments. The Kp value was used for scenarios with continuous contact to boron containing photochemicals (Scenarios A3, B3, C3, D3, C4, D4).

3. HUMAN EXPOSURE ASSESSMENT

Based on information provided by industry associations (e.g. EPIA 2009a,b,c, I&P Europe 2010a,b, see Annex III), literature screening (e.g. internet) and guidance on application of consumer photochemicals retrieved from representative Safety Data Sheets, exposure scenarios for consumers were developed and exposure levels derived. For data gaps default values and conservative estimates were introduced. No studies and models are available for the determination of the particular case of exposure of non-professionals to photographic chemicals. The use of personal protective equipment (PPE) and risk management measures (RMM) is not considered for consumers, even if they are recommended by the manufacturer. This is in line with ECHA guidance on Information Requirements and Chemical Safety Assessment, Chapter R15.

Exposures to boric acid and borates are expressed in terms of boron (B) equivalents based on the content of boron of the substance on a molecular weight basis. The rationale for this approach is detailed in the introduction. The conversion factors can be retrieved from table 1.

Two approaches per scenario are presented:

The first approach is the “typical case” based inter alia on the data provided by EPIA and I&P. It represents the expected, typical exposure level of the scenario referring to conservative values within the given variability of data as well as to standard default values.

As every scenario reveals uncertainties which are not covered by the available data (e.g. different hygiene of users during application, different durations of time needed for a particular task, different exposure rates, incorrect - maybe improper - handling, possible increase of boron content in future photochemicals in comparison with the currently available products), a second approach intended as a “reasonable worst case” (RWC) of the same scenario is presented to cover these uncertainties on possible exposures and risks. Risk characterisation ratios are presented for both approaches.

Despite these considerations, it has to be stressed that higher exposure levels via the use of photochemicals are conceivable, but are not considered as these scenarios would result from unforeseen applications of the products (e.g. use of the photochemical products for other purposes

than the processing of photographic films). Poisoning of general public, including oral uptake by children, is considered as an exceptional case and therefore is not within the scope of this evaluation.

3.1 Identification of main exposure routes for human exposure towards boron from its use in photographic applications

Boron compounds are readily absorbed orally and by inhalation as demonstrated by numerous studies reporting increased levels of boron in blood, tissues, or urine after exposure via both routes (Austria, 2009). For the present evaluation absorption rates for oral and inhalation route are assumed to be 100%.

Dermal absorption is considered to be 0.5%. This value is used to assess the dermal absorption of solids on skin and is applied for Scenarios B1 and D1 covering the preparation of solutions from powder formulations via dust release into the air. During the preparation of diluted solutions from liquid concentrates and the use of prepared solutions for tank development of films (Scenarios A1, A2, B2, C1, C2, D2), dermal exposure to the liquids is expected to be short as the involved pouring tasks are not expected to last longer than a few minutes. It is assumed that liquids dry on skin within a short time and solid residues remain. A dermal absorption value of 0.5% is applied, washing of the hands is not considered for this scenario.

A permeability (Kp) of 2.0 x 10^{-4} cm/h is used in scenarios A3, B3, C3, C4, D3 and D4, which cover photographic processing in trays with continuous contact to solutions. This value was derived from the in vitro study by Wester et al. (1998) using an exposure time of four hours (see table I and section 2.4 on dermal absorption). The product of permeability and concentration corresponds to the flux of boron through the skin (Kp x C = flux).

The main routes of human exposure to boron originating from the application of photochemicals and the corresponding absorption values are listed in table I below. Inhalative and dermal exposure of non-professionals to boron is possible during the preparation/use and disposal of photographic solutions. Oral exposure is not relevant for consumers, as misuse (e.g. oral uptake by children) is not covered by this assessment.

Table I: Main paths of human exposure to boron via photographic solutions (for details on toxicokinetics see section on dermal absorption and Austria (2009))

Exposure path	Absorption	Human exposure during preparation of solutions intended for photographic applications
Inhalation	100%	Yes
Dermal (for dry powder or dried liquid)	0.5%	Yes
Dermal (penetration from liquids under conditions with permanent skin contact to the liquid)	Kp = 2.0 x 10^{-4} cm/h	Yes
Oral	100%	Not relevant

3.2 Human exposure of non-professional users during application of boron-containing photochemicals

3.2.1 Exposure Scenarios

Referring to information provided by EPIA and I&P Europe, boron is present in some of the following currently available products, which are intended as photographic chemicals for non-professionals:

- Film developers: supplied as liquid concentrates (Scenario A), powder formulations (Scenario B) and ready-to-use solutions
- Fixers (intended for the development of films and papers): supplied as liquid concentrates (Scenario C), powder formulations (Scenario D) and ready-to-use solutions

Exposures to the ready-to-use solutions are considered to be covered by the scenarios describing the use of liquid concentrates and powder formulations, as the application for photographic processing is considered to be similar to these scenarios except for the absence of an activity of preparing working solutions.

The exposure scenarios for film developers and fixers are expected to be comparable to a great extent. Differences between developers/fixers and liquid concentrates/powder formulations are considered and refer to the boron content of the original product, boron concentration of the prepared solutions and frequency and duration of activities. As the handling and relevant exposure scenarios of film developers and fixers are assumed to be comparable, the same models of calculation can be applied.

Four product types are considered in general Scenarios:

Scenario A: Use of film developers solutions made from liquid concentrates

Scenario B: Use of film developers solutions made from powder formulations

Scenario C: Use of fixer solutions made from liquid concentrates

Scenario D: Use of fixer solutions made from powder formulations

These scenarios are subdivided based on preparation and use of the product types:

Pouring liquid concentrates into container (A1, C1)

Pouring powder formulations into container (B1, D1)

Tank processing (A2, B2, C2, D2)

Tray processing of films (A3, B3, C3, D3)

Tray processing of papers (C4, D4)

3.2.2 Scenarios A1 and C1 - Pouring liquid concentrates into container

General description: Liquid concentrates (film developers and fixers) are supplied in a form requiring dilution before use. A typical dilution is 1+4; one part (by volume) of the concentrate is mixed with four parts (by volume) of water. On a small scale, this would typically be done using a measuring container. Inhalation exposure is disregarded as no mists or aerosols are generated during these tasks and gaseous releases are low (indicated by high water solubilities of borate compounds and low vapour pressures of the pure substances, which is typical for solid compounds with high melting points). Even in the case of saturated air (max. possible concentration as gas in air), the concentration in air and thus exposure via inhalation would be low (negligible in comparison to the other sources of exposure). It is assumed, that dermal exposure is the most relevant route for the use of liquid concentrates and subsequent handling of prepared solutions. The applied model relies on the thin-layer model, which is recommended as Tier 1 model for the instant application of a substance contained in a preparation within the ECHA guidance on IR and CSA, Chapter R15.

Typical exposure level: Potential dermal exposure due to spillages is possible during pouring of the concentrate into the container. It is assumed that the operator contaminates a surface area of 420 cm^2 of his skin with the concentrate during preparation (touching contaminated surfaces, spillages spread over skin, etc.). 420 cm^2 complies with the total surface area of one hand respectively with the surface area of the palms (respectively backs) of both hands (420 cm^2-default value). The applied boron concentrations and the given densities of the solutions are based on data provided by I&P Europe and EPIA: 0.46 % for fixers (I&P Europe 2010), 0.85% for film developers (EPIA 2009c). To cover the variation of the available liquid concentrates, the maximum values of the given concentration data are taken.

Worst case approach: For this calculation contamination of 840 cm^2 skin area is assumed. This value covers uncertainty by possible improper handling by the consumer resulting in exposure of the total surface area of both hands. Alternatively it would cover preparation of two stock solutions per day instead of one (2 x exposure of 420 cm^2) in the case of losing a prepared solution due to improper handling, e.g. due to spillage. Furthermore, a boron content of 1% of the concentrate instead of 0.85% respectively 0.46% (A1 and C1) is assumed which is the maximum possible boron content based on the solubility of the boron compounds subject to this assessment in aqueous photographic solutions (EPIA 2009a, see section on 5.2.3). This should cover uncertainties with regard to boron concentrations in possible future products.

Table II reveals the calculation of Scenario A1 covering the preparation of diluted film developer solutions made from liquid concentrates.

Table III reveals the calculation of Scenario C1 covering the preparation of diluted fixer solutions made from liquid concentrates.

	Table II: Dermal exposure via Scenario A1 Pouring liquid film developer concentrates into container		**Table III: Dermal exposure via Scenario C1 Pouring liquid fixer concentrates into container**	
	Typical exposure	Worst-case exposure	Typical exposure	Worst-case exposure
User	Non-professional	Non-professional	Non-professional	Non-professional
Bodyweight- BW [kg]	60	60	60	60
Frequency of event- F [1/d]	1	1	1	1
Boron-concentration- BC [%w/w]	0.85	1	0.46	1
Density of solution- ρ [mg/cm^3]	1300	1300	1350	1350
Surface-area exposed per event-SA [cm^2]	420	840	420	840
Thickness of liquid film on skin-Th [cm]	0.01	0.01	0.01	0.01
Dermal absorption- DA [%]	0.5	0.5	0.5	0.5
Systemic exposure-SE [mg B/kg bw/d]	0.0039	0.0091	0.0022	0.0095
Calculation	F x BC/100 x ρ x SA x Th x DA/100 /BW = SE			

3.2.3 Scenarios B1 and D1: Pouring of powder formulations into a container

General description: Powder formulations (film developers and fixers) need to be dissolved in water before use (Scenarios B1 and D1). Exposure occurs when pouring the powder into the receiving container to make a "stock" solution, either by skin contact or by inhalation of dust. During subsequent stirring and mixing no airborne dust is generated, as the powders are readily wet and dispersed on contact with water. Inhalation exposure via gaseous releases can also be disregarded as the vapour pressure of the substances in water is expected to be low and generation of mists or aerosols does not take place (see explanation 3.2.2).

The pouring of the powders is expected to be performed indoors and in the absence of local exhaust ventialation. As no personal sampling data (see also 5.2.5) or suitable models are available, EASE (EUSES 2.1) has been used to estimate inhalation and dermal exposure ranges for this activity. The parameters used for inhalation exposure are: a non fibrous dust, dry manipulation, no LEV and a non-readily aggregating dust. Assuming these conditions, EASE gives an exposure range of 5 to 50 mg dust per m^3. The max. value of 50 mg dust per m^3 is taken forward for the RWC-approach and the arithmetic mean of 27.5 mg/m^3 for the typical approach. The parameters used for dermal exposure were dusty solid, non-dispersive use and direct handling with incidental contact. The estimated exposure range for these parameters is 0.0 to 0.1 mg/cm^2/day. The max. value of 0.1 mg/cm^2/day is taken forward for the RWC-approach and the arithmetic mean of 0.05 mg/cm^2/day for the typical approach.

Based on a dermal absorption fraction of 0.5% derived from the in vivo part of Wester et al. (1998), it is assumed that 0.5% of the boron deposited on skin during the exposure time is absorbed. Calculation of inhalation exposure relies on the corresponding Tier 1 model within the ECHA guidance on IR and CSA, Chapter R15.

Typical exposure level: Amateur users of powder formulations will normally produce sufficient solution to allow several respectively all planned events of photographic processing on a single day. Therefore, the number of events of preparing diluted solutions will typically be one event per day (EPIA 2009b). Potential dermal and inhalation exposures via airborne dust are possible during pouring of the powder into the receiving container. Dust concentration in air during this task is expected to be typically 27.5 mg/m^3 for 15 minutes. It is expected that the total surface area of the hands is exposed (default, 840cm^2). The applied boron concentrations of the powder formulations are based on industry data: 5.5% for film developers (EPIA 2009c) and 0.18% for fixers (I&P Europe 2010a).

Worst-case approach: A contamination of 4370 cm^2 is assumed referring to the surface area of upper extremities and face of an adult (default values, table R.15-7; ECHA guidance on IR and CSA, Chapter R15) to cover uncertainty on exposed surfaces in the case of improper handling respectively on powder formulations revealing a high dustiness. Furthermore, two preparation events per day instead of one are considered to cover uncertainty in the case of losing a prepared solution due to improper handling (e.g. due to spillage). Based on the current knowledge it cannot be excluded that products containing a higher boron content than identified as the maximum concentration in currently available powder products will be placed on the market in the future. To cover this possibility B-contents of 10% (film developers) and 0.5% (fixers) are used as estimated notional values.

Table IV reveals the calculations for Scenario B1 covering the preparation of developer solutions from powder formulations.

Table V reveals the calculations for Scenario D1 covering the preparation of fixer solutions from powder formulations.

	Table IV		Table V	
Scenario and Route	**Dermal exposure via Scenario B1: Pouring of film developer powder formulations into a container**		**Dermal exposure via Scenario D1: Pouring of fixer powder formulations into a container**	
	Typical exposure	Worst-case exposure	Typical exposure	Worst-case exposure
User	Non-professional	Non-professional	Non-professional	Non-professional
Bodyweight- BW [kg]	60	60	60	60
Frequency of event- F[1/d]	1	2	1	2
Boron-concentration- BC [%w/w]	5.5	10	0.18	0.5
Surface-area exposed per event-SA [cm^2]	840	4370	840	4370
Dust deposition-DD [$mg/cm^2/d$]	0.05	0.1	0.05	0.1
Dermal absorption- DA [%]	0.5	0.5	0.5	0.5
Systemic exposure- SE [mg B/kg bw/d]	0.0002	0.0073	0.00001	0.00036
Calculation	F x BC/100 x SA x DD x DA/100 /BW = SE			
Scenario and route	**Inhalative exposure via Scenario B1: Pouring of film developer powder formulations into a container**		**Inhalative exposure via Scenario D1: Pouring of fixer powder formulations into a container**	
	Typical exposure	Worst-case exposure	Typical exposure	Worst-case exposure
User	Non-professional	Non-professional	Non-professional	Non-professional
Bodyweight- BW [kg]	60	60	60	60
Respiration rate- RR [m^3/h]	1.25	1.25	1.25	1.25
Frequency of event- F [1/d]	1	2	1	2
Duration of event- D [h]	0.25 (15 min)	0.25 (15 min)	0.25 (15 min)	0.25 (15 min)
Boron-concentration- BC [%w/w]	5.5	10	0.18	0.5
Dust concentration- DC [mg/m^3]	27.5	50	27.5	50
Inhalation absorption- IA [%]	100	100	100	100
Systemic exposure- SE [mg B/kg bw/d]	0.0079	0.0521	0.0003	0.0026
Calculation	F x BC/100 x DC x IA x RR x D /BW = SE			

3.2.4 Scenarios A2, B2, C2 and D2- Tank processing

General description: The most common application for the preparation of films among consumers is the use of developing tanks. The films are put in a light-tight container. This allows the operator to develop photographic films in day light environment. The photographic solutions as developers, stop bath and fixers are added and removed one after another. During film development the filled tank is continuously shaken/ moved thoroughly in order to distribute the developer/fixer evenly. During the shaking process (either manual or automatic) the tank is closed. Exposure of the user is therefore not expected. Potential exposure to the prepared solutions is only possible during filling and disposal (Ilford 2004, Kodak 2007).

The applied model is based on the thin-layer model, which is recommended as a Tier 1 model for the instant application of a substance contained in a preparation within ECHA guidance on IR and CSA, Chapter R15.

Typical exposure level: Depending on the type of the tank and on the size of the films, one or more films can be placed in one tank. It is assumed that a developer tank is prepared two times per day for film/paper processing. Dermal exposure is possible to occur during filling/emptying of the developer tanks before/after applying the prepared solutions (film developer, fixer). It is assumed, that 840 cm^2 skin are contaminated during these two steps of pouring liquid (840 cm^2 as default surface area for two hands). No continuous contact of skin with the solutions is assumed for these calculations. The presented boron concentrations (0.17% and 0.23% for Scenarios A2 and B2, 0.09% and 0.03% for Scenarios C2 and D2) and densities of the prepared solutions are based on data provided by EPIA (2009c) and I&P Europe (2010a) and represent maximum values referring to the recommended dilutions given within the instruction leaflets of the suppliers.

Worst case approach: Four instead of two tank development preparations per day are assumed in contrast to the typical scenario. According to I&P Europe, there is no practical advantage of using film developer solutions containing higher boron concentrations than the given values of 0.17% and 0.23% (Scenarios A2 and B2) (I&P Europe 2010b). Therefore, no uncertainty on future boron concentrations is considered in the worst- case approach. To cover uncertainty on possible higher boron concentrations of prepared fixer solutions in future products, a content of 0.2% boron is considered as a notional and worst-case value for prepared fixer solutions (scenarios C2 and D2) (see section 5.2.3).

Table VI reveals the calculations for Scenarios A2 (liquid concentrates) and B2 (powder formulations) covering the use of prepared film developer solutions for tank development.

Table VII reveals the calculations of Scenarios C2 (liquid concentrates) and D2 (powder formulations) covering the use of prepared fixer solutions for tank development.

	Table VI: Dermal exposure via A2 and B2: Use of film developers for tank development		**Table VII: Dermal exposure via C2 and D2 Use of fixers for tank development**	
	Typical exposure	Worst-case exposure	Typical exposure	Worst-case exposure
User	Non-professional	Non-professional	Non-professional	Non-professional
Bodyweight [kg]	60	60	60	60
Frequency of event [1/d]- F	2	4	2	4
Boron-concentration [%w/w]- BC	0.17 | 0.23 [A2 | B2]	0.17 | 0.23 [A2 | B2]	0.09 | 0.03 [C2 | D2]	0.20 | 0.20 [C2 | D2]
Density of solution-ρ [mg/cm^3]	1060	1060	1090 | 1070 [C2 | D2]	1090 | 1070 [C2 | D2]
Surface-area exposed per event- SA [cm^2]	840	840	840	840
Thickness of liquid film on skin- Th [cm]	0.01	0.01	0.01	0.01
Dermal absorption- DA [%]	0.5	0.5	0.5	0.5
Systemic exposure- SE [mg B/kg bw/d]	0.0025 | 0.0034 [A2 | B2]	0.0050 | 0.0068 [A2 | B2]	0.0014 | 0.0004 [C2 | D2]	0.0061 | 0.0060 [C2 | D2]
Calculation	F x BC/100 x ρ x SA x Th x DA/100 /BW = SE			

3.2.5 Scenario A3, B3, C3 and D3- Film processing in trays

3.2.5.1 Scenario A3 and B3: Application of film developer solutions for processing in trays

General description: Tray development is the most economic way of processing sheet films. This processing has to be done in complete darkness. The films are introduced by hand which results in the immersion of parts of the hands at each stage of the process (development, stop bath, fixation). Continuous or intermittent agitation has to be assured while the sheets are in contact with the developer solution. If the sheets are developed one by one, this can be assured by moving the tray. In this case the scenario involves possible hand contact with the developer solution when introducing the sheet and when taking it out. Pressing down the sheet with one hand after introduction may also be possible. For processing more than one film sheet at a time, "shuffle agitation" can be practised (Anchor et al. 1998, Dhananjay 1999, Schaefer 1999, Wikipedia 2010 and Park, You Tube, 2010). The sheets are introduced one by one into the developer solution. Then they are moved during the whole development time by lifting the sheet at the bottom of the sheet track to the top in a constant rhythm.

Tray development results in longer durations of contact of the operator with the solutions than in the case of tank development (up to several hours per day). In order to consider the kinetic of dermal boron absorption from continuous contact to solutions, the dermal exposure resulting from this scenario is described using a Kp (permeability) of 2.0×10^{-4} cm/h, which is calculated from the results of an infinite dosing experiment (See section 2.4 on dermal absorption). The product of Kp and concentration corresponds to the flux of boron through the skin (Kp x C = flux).

Typical exposure level: Based on fact sheet data (Ilford 2004), 10 min development time can be considered as a typical value, this results in 10 min dermal contact with the solutions per cycle. Two cycles per day (task: about 2 hours, dermal exposure: 20 min) are estimated to be representative. The contaminated surface area of the operator's skin is expected to be 420 cm^2 and to be continuously exposed to the diluted solution. 420 cm^2 comply with the surface area of one hand, respectively of two half hands. The concentration of the prepared solutions is estimated to be 0.17%, if they are prepared from liquid concentrates (EPIA 2009c, maximum value) and to be 0.23%, if they are prepared from powder formulations (I&P Europe 2010a, maximum value). Dermal contamination during pouring and removing solutions is considered to be already covered by this scenario. The use of gloves or tweezers is not considered.

Worst-case approach: To cover uncertainty on use frequency, four cycles per day are considered (four hours of developing films instead of two), resulting in 80 minutes of continuous contact to the diluted solution. Furthermore, to cover uncertainty on exposed surfaces, it is anticipated that the operator uses both hands to move the films in the solutions (840 cm^2).

Table VIII reveals the calculations of Scenarios A3 (liquid concentrates) and B3 (powder formulations) covering the use of prepared film developer solutions for development in trays.

Table VIII: Dermal exposure via Scenarios A3 and B3 (solutions made from liquid concentrates/powder formulations) **Use of film developers for tray processing**		
	Typical exposure	Worst-case exposure
User	Non-professional	Non-professional
Bodyweight- BW [kg]	60	60
Frequency of event- F [1/d]	1	1
Contact time- CT[h]	0.33 (20 min)	1.33 (80 min)
Surface-area exposed - SA [cm^2]	420	840
Density of solution- ρ [mg/cm^3]	1060	1060
Permeability- Kp [cm/h]	2.0×10^{-4}	2.0×10^{-4}
B-Concentration- C [%w/w]		
Scenario A3 (Liquid concentrates)	0.17	0.17
Scenario B3 (Powder formulations)	0.23	0.23
Systemic exposure- SE [mg B/kg bw/d]		
Scenario A3 (Liquid concentrates)	0.0008	0.0067
Scenario B3 (Powder formulations)	0.0011	0.0091
Calculation	F x CT x SA x ρ x Kp x C/100 /BW = SE	

3.2.5.2 Scenarios C3 and D3: Application of fixers for film processing

General description: A recommended and efficient method of fixing film (or paper) is to use the two bath fixing technique. Two separate fixing baths of the same volume are prepared. The film is fixed in the first bath for half of the recommended fixing time and then transferred to the second bath for the remaining time. Work is continued this way until the capacity of the first bath is reached, and then it is discarded and replaced with the second fixer bath. A completely fresh second bath is prepared and used. This process is repeated as required with the result that the film or paper is always thoroughly fixed by the relatively fresh fixer in the second bath (Ilford 2002).

2 to 5 minutes of fixing time per cycle are recommended without hardener and 4 to 10 minutes per cycle with hardener (Ilford 2002). Based on these values, 10 minutes per cycle are taken for the calculation of the reasonable worst case approach and 7 minutes per cycle (average value of 4 and 10 minutes) for the typical approach.

As the users are expected to be continuously exposed to fixer solution for significant durations of time, dermal exposure is determined on the basis of the skin permeability value Kp derived for Scenarios A3 and B3 (Kp: 2.0×10^{-4} cm/h).

Typical exposure level: The contaminated surface area during this task is expected to be 420 cm^2. 420 cm^2 comply with the surface area of one hand respectively of two half hands. The size of this surface seems to be justified considering spillages due to possibly quick movements within the tray and the possibility of using both hands for handling several films (see references for Scenarios A3 and B3). The concentrations of the prepared fixer solutions are 0.09% ($\rho \sim 1090$ mg/cm^3), if they are prepared from liquid concentrates and to be 0.03% ($\rho \sim 1070$ mg/cm^3), if they are prepared from powder formulations. These values are based on data provided by I&P Europe (2010a) and refer currently to only two products (one fixer supplied as powder and one as liquid concentrate). Two cycles per day are assumed to be typical complying with two hours of processing (see Scenarios A3 and B3). Considering a fixing time of 7 minutes per cycle this results in 14 minutes of contact with the solution. The use of gloves or tweezers is not considered.

Worst-case approach: To cover uncertainty on use frequency and duration of fixing, four cycles of fixing films per day and a fixing time of 10 minutes per cycle are considered (four hours of film processing instead of two; see Scenario A3 and B3), resulting in 40 minutes of continuous contact with the prepared fixer solutions. Furthermore, to cover uncertainty on the size of exposed skin, it is anticipated that the operator uses both hands to move the films in the solutions and that they are totally exposed during this activity (840 cm^2). The concentration of the fixer solutions (made from liquid concentrates and powder formulations) is assumed to be 0.2% for both products. 0.2% is a notional value (~ double as high as 0.09% for being conservative) (see section 5.2.3).

Table IX reveals the calculations of Scenarios C3 (liquid concentrates) and D3 (powder formulations) covering the use of prepared fixer solutions for film processing in trays.

3.2.6 Scenarios C4 and D4: Application of fixers for paper processing

General description: As for Scenarios C3 and D3 the two bath fixing technique is assumed to be a representative exposure scenario. Referring to Ilford (2002) 0.5 to 2 minutes of fixing time per cycle are recommended. Referring also to representative fact sheets, development times of papers are in the range of a few minutes. The fact sheet "b&w paper developers" (Ilford, January 2004) recommends development times from 1 to 3 minutes, 10 seconds in the stop bath and at least 30 seconds of washing papers in running water. Based on this information, it is assumed that one third of the duration of one cycle is spent on the fixation of papers as a conservative estimate. Assuming 2 hours of paper processing as typical and 4 hours as a reasonable worst case (breaks and other tasks are not considered), this results in 40 minutes respectively 80 minutes of using the fixer.

Typical exposure level: It is assumed that the operator uses one hand to place papers into the fixer solution resulting in dermal contact with the liquid. Furthermore, it is expected that the papers are moved with the fingers of one hand or the trays are moved manually. Continuous or intermittent agitation has to be assured while the sheets are in contact with the fixer solution. Referring to the fixing times of a few minutes, it is estimated that the contaminated skin area remains wet during the whole time of fixation. The exposed size of skin is estimated to be 210cm^2 complying with the surface area of the half of one hand (fingers). As already explained above, 40 minutes of contact time with the fixers are assumed.

Worst-case approach: To cover uncertainty on the duration of handling fixers, 80 minutes of exposure time are taken forward referring to 4 hours of paper processing. Furthermore, it is anticipated that the operator uses both hands for placing and moving the papers in the solutions and that 420 cm^2 skin are exposed. The concentration of the fixer solutions (made from liquid concentrates and powder formulations) is assumed to be 0.2% for both products. 0.2% is a notional value (~ double as high as 0.09% for being conservative) (for further information see section 5.2.3).

Table X reveals the calculations of Scenarios C4 (liquid concentrates) and D4 (powder formulations) covering the use of prepared fixer solutions for paper processing in trays. The densities and boron concentration are the same as for the Scenarios C3 and D3.

Table IX: Derm. exposure via Scenarios C3 and D3 **Use of fixers for film processing in trays**		
	Typical exposure	Worst-case exposure
User	Non-professional	Non-professional
Bodyweight- BW [kg]	60	60
Frequency of event- F [1/d]	1	1
Contact time- CT[h]	0.23 (14 min)	0.67 (40 min)
Surface-area exposed per event- SA [cm^2]	420	840
Density of solution- ρ [mg/cm^3]		
Scenario C3 (Liquid concentrates)	1090	1090
Scenario D3 (Powder formulations)	1070	1070
Permeability- Kp [cm/h]	2.0×10^{-4}	2.0×10^{-4}
B-Concentration- C [%w/w]		
Scenario C3 (Liquid concentrates)	0.09	0.20
Scenario D3 (Powder formulations)	0.03	0.20
Systemic exposure- SE [mg B/kg bw/d]		
Scenario C3 (Liquid concentrates)	0.0003	0.0041
Scenario D3 (Powder formulations)	0.0001	0.0040
Calculation	F x CT x SA x ρ x Kp x C/100 /BW = SE	

Table X: Derm. exposure via Scenarios C4 and D4 **Use of fixers for paper processing in trays**		
	Typical exposure	Worst-case exposure
User	Non-professional	Non-professional
Bodyweight- BW [kg]	60	60
Frequency of event- F [1/d]	1	1
Contact time- CT[h]	0.67 (40 min)	1.33 (80 min)
Surface-area exposed per event- SA [cm^2]	210	420
Density of solution- ρ [mg/cm^3]		
Scenario C4 (Liquid concentrates)	1090	1090
Scenario D4 (Powder formulations)	1070	1070
Permeability- Kp [cm/h]	2.0×10^{-4}	2.0×10^{-4}
B-Concentration- C [mg/cm^3]		
Scenario C4 (Liquid concentrates)	0.09	0.20
Scenario D4 (Powder formulations)	0.03	0.20
Systemic exposure- SE [mg B/kg bw/d]		
Scenario C4 (Liquid concentrates)	0.0005	0.0041
Scenario D4 (Powder formulations)	0.0001	0.0040

3.2.7 Consumer exposure during use of boron-containing photochemicals

Development of films in trays (A3, B3, C3 and D3) is less widespread among consumers than tank development of films, as the relevant procedures are time consuming and complex

Table XI: Film developers: Total human exposure during application of liquid concentrates (Scenario A)

Combined Scenarios Application of film developers made from liquid concentrates		Estimated Internal Exposure [mg/kg bw/day]			
		Inhal. uptake	Dermal uptake	Oral uptake	Combined exposure
Liquid concentrate - Scenario A1: Pouring concentrate into receiving container	Typical exposure level	-[1]	0.0039	-[1]	0.0039
	Worst case exposure level	-[1]	0.0091	-[1]	0.0091
Diluted solution - Scenario A2: Tank Processing	Typical exposure level	-[1]	0.0025	-[1]	0.0025
	Worst case exposure level	-[1]	0.0050	-[1]	0.0050
Diluted solution - Scenario A3: Processing of films in trays	Typical exposure level	-[1]	0.0008	-[1]	0.0008
	Worst case exposure level	-[1]	0.0067	-[1]	0.0067
The combination of Scenario A1 and A2 results in a typical exposure level of and in a worst case exposure level of					0.0064 0.0141
The combination of Scenario A1, A2 and A3 results in a typical exposure level of and in a worst case exposure level of					0.0072 0.0209

[1] This route of exposure is expected to be not relevant for the referring task

Table XII: Film developers: Total human exposure during application of powder formulations (Scenario B)

Combined Scenarios Application of film developers made from powder formulations		Estimated Internal Exposure [mg/kg bw/day]			
		Inhal. uptake	Dermal uptake	Oral uptake	Combined exposure
Powder formulation - Scenario B1: Pouring powder formulation into receiving container	Typical exposure level	0.0079	0.0002	-[1]	0.0081
	Worst case exposure level	0.0521	0.0073	-[1]	0.0594
Prepared solution - Scenario B2: Tank processing	Typical exposure level	-[1]	0.0034	-[1]	0.0034
	Worst case exposure level	-[1]	0.0068	-[1]	0.0068
Prepared solution - Scenario B3:	Typical exposure level	-[1]	0.0011	-[1]	0.0011

Processing of films in trays	Worst case exposure level	-[1]	0.0091	-[1]	0.0091
The combination of Scenario B1 and B2 results in a typical exposure level of and in a worst case exposure level of					0.0115 0.0662
The combination of Scenario B1, B2 and B3 results in a typical exposure level of and in a worst case exposure level of					0.0126 0.0753

[1] This route of exposure is expected to be not relevant for the referring task

Table XIII: Fixers: Total human exposure during application of liquid concentrates (Scenario C)

Combined Scenarios Application of fixers made from liquid concentrates		**Estimated Internal Exposure [mg/kg bw/day]**			
		Inhal. uptake	**Dermal uptake**	**Oral uptake**	**Combined exposure**
Liquid concentrate - Scenario C1: Pouring concentrate into receiving container	Typical exposure level	-[1]	0.0022	-[1]	0.0022
	Worst case exposure level	-[1]	0.0095	-[1]	0.0095
Diluted solution - Scenario C2: Tank processing	Typical exposure level	-[1]	0.0014	-[1]	0.0014
	Worst case exposure level	-[1]	0.0061	-[1]	0.0061
Diluted solution - Scenario C3: Processing of films in trays	Typical exposure level	-[1]	0.0003	-[1]	0.0003
	Worst case exposure level	-[1]	0.0041	-[1]	0.0041
Diluted solution - Scenario C4: Processing of papers in trays	Typical exposure level	-[1]	0.0005	-[1]	0.0005
	Worst case exposure level	-[1]	0.0041	-[1]	0.0041
The combination of Scenario C1, C2 and C3 results in a typical exposure level of and in a worst case exposure level of					0.0039 0.0196
The combination of Scenario C1, C2 and C4 results in a typical exposure level of and in a worst case exposure level of					0.0040 0.0196

[1] This route of exposure is expected to be not relevant for the referring task

Table XIV: Fixers: Total human exposure during application of powder formulations (Scenario D)

Combined Scenarios Application of fixers made from powder formulations		**Estimated Internal Exposure [mg/kg bw/day]**			
		Inhal. uptake	**Dermal uptake**	**Oral uptake**	**Combined exposure**
Powder formulation - Scenario D1: Pouring	Typical exposure level	0.0003	0.00001	-[1]	0.00026

powder into receiving container	Worst case exposure level	0.0026	0.00036	-[1]	0.00297
Prepared solution - Scenario D2: Tank processing	Typical exposure level	-[1]	0.0004	-[1]	0.0004
	Worst case exposure level	-[1]	0.0060	-[1]	0.0060
Prepared solution - Scenario D3: Processing of films in trays	Typical exposure level	-[1]	0.0001	-[1]	0.0001
	Worst case exposure level	-[1]	0.0040	-[1]	0.0040
Prepared solution - Scenario D4: Processing of papers in trays	Typical exposure level	-[1]	0.0001	-[1]	0.0001
	Worst case exposure level	-[1]	0.0040	-[1]	0.0040
The combination of Scenario D1, D2 and D3 results in a typical exposure level of and in a worst case exposure level of					0.0008 0.0130
The combination of Scenario D1, D2 and D4 results in a typical exposure level of and in a worst case exposure level of					0.0009 0.0130

[1] This route of exposure is expected to be not relevant for the referring task

3.3 Exposure of general public via environment

Boron is a naturally occurring element and significant amounts can be found in human food and drinking water representing major sources of exposure. Boron enters the environment mainly through weathering of rocks, boric acid volatilization from seawater and volcanic activity, to a lesser extent it is also released from anthropogenic sources. Anthropogenic sources include agriculture, refuse, fuel and wood burning, power generation using coal and oil, glass product manufacture, use of borates/perborates in home and industry, borate mining/processing, leaching of treated wood/paper and sewage/sludge disposal.

According to Austria (2009) and other assessments (e.g. WHO, 1998), it is estimated that food and drinking water contribute nearly 100% to the human boron uptake via the environment, whereas exposure via air and ingestion of soil are comparatively low and can be neglected.

Rich sources of boron are generally fruits, vegetables, pulses, legumes and nuts. Significant amounts can also be found in coffee and wine. Comparatively high boron contents can also be present in drinking water and mineral water, depending on their origin. Dairy products, fish, meat and most grains are poor sources of boron. The following exposure levels of boron via food and drinking water are applied for this assessment (source: Austria, 2009).

Total daily boron uptake of man via food and drinking water:

Typical: 2.3-2.74 mg B/person/day (0.038 – 0.046 mg B/kg bw/day[*])

RWC: 3.5 – 3.94 mg B/person/day (0.058 – 0.066 mg B/kg bw/day[*])

[*]These values refer to a body weight of 60kg (default, adult)

The uptake can differ significantly, depending on the origin of food/water and the diet habits of individuals. Therefore, it cannot be excluded that even higher exposures to boron via food and drinking water can occur.

4 RISK CHARACTERISATION OF APPLICATION OF BORON-CONTAINING PHOTOGRAPHIC CHEMICALS AND MAN VIA ENVIRONMEN

Risk characterisation ratios (RCRs) for the human health section are derived by comparing exposure levels to derived no-effect levels (DNELs) and express the risk to man resulting from the expected exposure levels. The following equation is used to describe this relation.

$$RCR = \frac{Exposure\ to\ boron\ (mg/kg\ bw/d)}{DNEL\ (mg/kg\ bw/d)}$$

RCRs are positive and dimensionless values (>0). Control of risk for a substance is demonstrated when the RCRs for all exposures from all exposure scenarios, all endpoints, all timescales and all exposed populations are below one (Exposure < DNEL).

A General Population-DNEL long term systemic of 0.096 mg B/kg bw/day for developmental effects was derived within this assessment. Referring to the bodyweight of an adult (60kg, default value), this is equal to 5.76 mg boron per day.[1]

The determined exposure levels of the derived scenarios covering photographic applications as summarised in tables XI to XIV result in the following risk characterisation ratios. These ratios describe the risks resulting from consumer application of photochemicals only. Other boron sources are not considered.

Scenario A and B cover the use of film developers. Scenario C and D refer to the use of fixers for film respectively paper processing (see 3.2.1). They contain the tasks „preparation of working solutions" and "their application for tank respectively tray processing". The development of plane films in trays is time consuming and complex (Scenario A3, B3, C3, D3), therefore, this procedure is much less widespread among consumers than the development of films in tanks (Scenario A2, B2, C2, D2) and tray processing of papers (C4, D4). Therefore, combination of scenarios A1+A2, B1+B2, C1+C2+C4 and D1+D2+D4 covering only "preparation of working solutions", "tank processing of films" and "tray processing of papers"(only relevant for fixers) are expected to comply with the common use pattern of most consumers (see table below).

Table XV: Risk characterisation ratios of combined scenarios expected to occur frequently

Risk characterisation ratios[1] Scenarios		**Combined exposure [mg/kg bw/day]**	**RCR of scenario [ ]**
Film developer: liquid concentrates A1 + A2 Preparation + tank processing	Typical exposure level	0.0064	0.07
	Worst case exposure level	0.0141	0.15
Film developer: powder formulations B1 + B2 Preparation + tank processing	Typical exposure level	0.0115	0.12
	Worst case exposure level	0.0662	0.69
Fixer: liquid concentrates	Typical exposure level	0.0040	0.04

[1] It is acknowledged that the REACH guidance recommends route-specific RC, but in order to simplify the comparison with dietary exposure to boron, the present RC is rather based on the combined exposure and an oral systemic DNEL.

C1 + C2 + C4 Preparation + tank processing + tray processing (papers only)	Worst case exposure level	0.0196	0.20
Fixer: powder formulations D1 + D2 + D4 Preparation + tank processing + tray processing (papers only)	Typical exposure level	0.0009	0.01
	Worst case exposure level	0.0130	0.13

[1]Referring to a General Population-DNEL long term systemic of 0.096 mg B/kg bw/d

Nevertheless, it cannot be excluded that tank and tray development of films and papers takes place on one day. This could be relevant for a minor group of appliers. Therefore, the combination of the following scenarios covering use of film developers and fixers is presented.

Table XVI: Risk characterisation ratios: Application of liquid concentrates and powder formulations, including tray development of films.

Risk characterisation ratios[1] Scenarios		**Combined exposure[2] [mg/kg bw/day]**	**RCR of scenario [ ]**
Film developers Use of liquid concentrate Scenario A: A1 + A2 + A3	Typical exposure level	0.0072	0.08
	Worst case exposure level	0.0209	0.22
Film developers Use of powder formulations Scenario B: B1 + B2 + B3	Typical exposure level	0.0126	0.13
	Worst case exposure level	0.0753	0.78
Fixers: film processing Use of liquid concentrates Scenario C^F: C1 + C2 + C3	Typical exposure level	0.0039	0.04
	Worst case exposure level	0.0196	0.20
Fixers: paper processing Use of liquid concentrates Scenario C^P: C1 + C2 + C4	Typical exposure level	0.0040	0.04
	Worst case exposure level	0.0196	0.20
Fixers: film processing Use of powder formulations Scenario D^F: D1 + D2 + D3	Typical exposure level	0.0008	0.01
	Worst case exposure level	0.0130	0.13
Fixers: paper processing Use of powder formulations Scenario D^P: D1 + D2 + D4	Typical exposure level	0.0009	0.01
	Worst case exposure level	0.0130	0.13

[1]Referring to a General Population-DNEL long term systemic of 0.096 mg B/kg bw/d

[2]Consideration of all relevant exposure routes during the performance of a task.

The values describing exposure via environment were taken from Austria (2009, section on exposure if man via environment). A summary of the derived exposure levels is given in section

3.3. Referring to a General Population-DNEL long term systemic of 0.096 mg B/kg bw/d, they result in the following risk characterisation ratios.

Table XVII: Risk characterisation ratios: Exposure via food and drinking water

Risk characterisation ratios[1] Scenarios		**Exposure [mg/kg bw/day]**	**RCR [ ]**
Regional exposure of man via environment Typical values	Min. value	0.038	0.40
	Max. value	0.046	0.48
Regional exposure of man via environment Reasonable worst case values	Min. value	0.058	0.60
	Max. value	0.066	0.69

[1]Referring to a General Population-DNEL long term systemic of 0.096 mg B/kg bw/d

The combination of the "photographic-application-scenarios" with the "man via environment-scenarios" is done by summing up the relevant risk characterisation ratios (see tables XVIII and XIX). The max. values of 0.48 and 0.68 of the typical and the reasonable worst case range of man via environment are taken as representative estimates (see table. XVII). The RCR's of the "Photographic-Application-Scenarios" are taken from table XV and XVI.

Table XVIII: Risk characterisation ratios: Cumulative exposure to boron via photographic applications (frequent scenarios taken from table XV) and via environment (food and drinking water)

Combined scenarios of photographic processing[1]		RCR of photographic application scenario [mg/kg bw/day]	Cumulative RCR[2] + 0.48[1] [ ]	Cumulative RCR[2] +0.68[1] [ ]
Film developer: liquid concentrates A1 + A2 Preparation + tank processing	typical	0.07	0.54	0.75
	worst case	0.15	0.62	0.83
Film developer: powder formulations B1 + B2 Preparation + tank processing	typical	0.12	0.64	0.80
	worst case	0.69	1.17	1.37
Fixer: liquid concentrates C^P: C1 + C2 + C4 Preparation + tank processing + tray processing of papers	typical	0.04	0.52	0.73
	worst case	0.20	0.68	0.89
Fixer: powder formulations D^P: D1 + D2 + D4 Preparation + tank processing + tray processing of papers	typical	0.01	0.48	0.69
	worst case	0.13	0.61	0.82

[1]Referring to a General Population-DNEL-long term systemic of 0.096 mg B/kg bw/d

[2]Cumulative RCR refers to the combination of the RCRs of the photographic application scenarios with the man via environment-scenarios. Occupational exposure and exposure via other consumer products are not considered and included, but would further increase the cumulative RCRs.

Table XIX: Risk characterisation ratios: Cumulative exposure to boron via photographic applications (scenarios taken from table XVI) and via environment (food and drinking water)

Combined scenarios of photographic processing[1]		RCR of photographic application scenario [mg/kg bw/day]	Cumulative RCR[2] + 0.48[1] [ ]	Cumulative RCR[2] +0.68[1] [ ]
Film developers Use of liquid concentrate Scenario A: A1 + A2 + A3	typical	0.08	0.55	0.76
	worst case	0.22	0.69	0.90
Film developers Use of powder formulations Scenario B: B1 + B2 + B3	typical	0.13	0.61	0.82
	worst case	0.78	1.26	1.47
Fixers: film processing Use of liquid concentrates Scenario C^F: C1 + C2 + C3	typical	0.04	0.52	0.72
	worst case	0.20	0.68	0.89
Fixers: film processing Use of powder formulations Scenario D^F: D1 + D2 + D3	typical	0.01	0.48	0.69
	worst case	0.13	0.61	0.82

[1]Referring to a General Population-DNEL long term systemic of 0.096 mg B/kg bw/d

[2]Cumulative RCR refers to the combination of the RCRs of the photographic application scenarios with the man via environment-scenarios. Occupational exposure and exposure via other consumer products are not considered and included, but would further increase the cumulative RCRs.

Scenarios C^P and D^P are presented in table XVIII.

5 UNCERTAINTY ANALYSIS AND DISCUSSION OF INPUT PARAMETERS

5.1 Human Health Effects

5.1.1 Assessment factors:

Boron compounds are substances for which refinement of the default assessment factors for interspecies and intraspecies variability seems possible, as toxicokinetic differences between animal species and human individuals are reduced compared to other substances. Absorption of boron compounds is similar in rats and humans as well as among different individuals and boron distributes rapidly and evenly within the body water. Boron compounds are not metabolised, but differences for excretion of boron compounds were described. However, for a possible refinement of the default assessment factors additional data on toxicokinetic behaviour in rats and a detailed evaluation of the complete available toxikokinetic database would be necessary. As this was not possible in the limited time available for the request, default values for inter- and intraspecies differences were used for the present evaluation.

The use of the default values for inter- and intraspecies differences contributes to an overestimation of the risk. For more details see section 2.3 and Annex I.

5.1.2 Dermal absorption:

From the human in vivo study by Wester et al. (1998) a value of 0.5% absorption was taken forward to estimate exposure to dry powder or dried liquids. The same value was used in the Biocides Report (2009) as well as in Austria (2009). All available studies carried out on intact skin (human and experimental animals) indicate very low dermal absorption, which is also revealed by the fact that difficulties occurred when trying to detect the minimal increase of boron in urine after dermal administration of boron compounds.

However, it has to be emphasised that the study by Wester et al. (1998) has several shortcomings (see section 2.4) which introduces a high degree of uncertainty to the derived value of 0.5%. It appears that the excretion of dermally applied boron was not completed when the study was finalised, boron excretion before and after dose application exerted considerable variability and a large fraction of the applied dose was not recovered (see annex II).

It was decided not to divide the value of 0.5% derived from the 24 hours study in human volunteers in order to adapt it to the actual duration of the tasks in specific scenarios. This is because it is unknown how long the actual exposure duration of the probands in the in vivo study lasted. It was mentioned that 5 to 10% of test material was washed off the skin of the volunteers at the end of the experiment. Parts of the material might have been lost much earlier and were therefore not contributing to the dose for 24 hours.

Based on the described flaws of the in vivo study (i.e. high variability of the data, methodological problems, the fact that excretion of administered dose might not have been completed) higher absorption values are conceivable. Even minor increases in percent absorption can have considerable effects on the resulting risk characterisation ratio.

For exposure scenarios describing continuous exposure to boron containing photochemical liquids a Kp value was derived using the original data from the infinite dose in vitro study by Wester et al. (1998). Instead of the values from the 24 hour exposure experiment the data from the 4 hour experiment were used for this calculation. As permeability of the skin increased over the 24 hours exposure time it would be an overestimation of skin absorption if the value for 24 hours would be used for the derivation of the Kp value, because direct handling of photochemicals by consumers is not expected to exceed 4 hours per event. For scenarios with longer exposure durations appropriate time points should be chosen for Kp derivation. These values were not corrected for possible outliers. A re-evaluation of the study is therefore recommended for future assessments. For the calculation of Kp values it is not recommended to include the skin content (OECD, 2004). Rather high and variable amounts of boron were detected within the skin at the end of the experiment, therefore it might also be considered to carry out a new in vitro study for future evaluations.

The assessment of dermal absorption is based on a poor quality data base. Although an evaluation of the whole data base indicates that dermal absorption through intact skin is low there remains an uncertainty concerning the estimates used, which could lead to both, an underestimation and an overestimation of dermal absorption. It has to be noted that absorption through damaged skin is considerably higher.

5.2 Exposure Assessment

5.2.1 Use of “shuffle agitation method” for tray processing of films

According to I&P Europe (2010a), only 1% of consumer users of film use sheet film. Industry representatives also indicated that they were not aware that their consumers used the “shuffle agitation method” to process their films. In contrast to this information descriptions of the method were found in two manuals for photographic processing (Anchor et al. 1998, Schaefer 1999), on a website for large format photography (Dhananjay 1999), in a video instruction (Park, You Tube, 2010) and in Wikipedia (2010). Personal experience with the method was communicated by photographers in different internet fora (APUG 2002, APUG 2010, Large Format Photography Forum 2009). In contrast to the statement from industry representatives the above references support the conclusion that there are non-professional photographers who use this method as their standard procedure. In order to cover all realistic use situations, the method was considered in the exposure scenario for sheet film processing, in spite of the fact that this might cause overestimation of exposure for consumers who process film sheets with other equipment.

5.2.2 Dermal exposure modelling

For exposure to liquid spillages (Scenarios A1, A2, B2, C1, C2, D2) the thin-layer-model for the instant application of a substance contained in a preparation was applied according to ECHA guidance on Information Requirements and Chemical Safety Assessment, Chapter R15. For dermal contact to dusts (Scenarios B1, D1), dust deposition values given by EASE (EUSES 2.1) were taken forward for the calculation. Dermal absorption was considered with a dermal absorption fraction of 0.5% derived from the in vivo part of the study by Wester et al. (1998, see section 2.4). This value refers to an exposure time of 24 hours. If hygiene and awareness of the user was assumed to a certain degree, the deposited boron from solution spillages or powders would remain on skin for a much shorter time and the application of this value would possibly lead to considerable overestimation of exposures. However, the actual exposure duration in the experiment carried out by Wester et al. (1998) was most probably much shorter than 24 hours (for discussion of dermal absorption see section 5.1.2).

On the other hand, a forum thread concerning usage of gloves during photochemical processing revealed a large variety of consumer attitudes and behaviours concerning dermal contact to photochemicals (Flickr, 2009). Immediate washing of the hands with water cannot be expected in any case (e.g. using only a towel for rubbing the hands clean, if no running water is present).

The calculation model for continuous exposure to photographic solutions (Scenarios A3, B3, C3, C4, D3, D4) depends on concentrations, exposed surface area and the substance specific permeability coefficient (Kp), which was derived from infinite dosing in vitro experiments by Wester et al. (1998, see section 2.4). Application of the thin-layer model with the absorption fraction from the in vivo study by Wester et al. (1998) would have resulted in underestimations of exposure for scenarios with continuous contact to photographic solutions. The results of the infinite in vitro study by Wester et al. (1998) were considered to better describe skin absorption during continuous exposure to photographic solutions.

5.2.3 Boron content of products and prepared solutions

The data on boron concentrations of the products and prepared solutions are based on values provided by EPIA respectively I&P Europe which reveal “typical” and “maximum” values (see tables XXI to XXIV). I&P Europe represent 90% of the European photochemical industry. Therefore, their information on the presence of boron in photographic chemicals and boron concentrations in these products are only representative for their companies (see tables XVIII and

XXI), 10% of the products on the market are not covered. This uncertainty could lead to underestimation of exposures.

For the present evaluation maximum values were applied for the typical approaches and more conservative notional values were applied for the RWC-approaches. The applied concentrations for the typical approach are expected to cover the variation of concentrations of products on the market, this may possibly overestimate average consumer exposures. But as consumers are expected to use mostly the same products ("brand loyalty") and the same dilution/concentration of the prepared solutions, it is possible that the same consumers are always exposed to the same and possibly high concentrated products/prepared solutions during photographic processing.

No quantitative information on the produced amounts of the single products was available. Therefore, it was not possible to estimate how many consumers are exposed to products with high boron concentrations respectively low boron concentrations. Although the given typical concentrations indicate the concentration of the currently most widespread product(s), it is not clear, how much of higher concentrated and the maximum concentration products are sold (maybe up to 49%- e.g. 2 products available). Therefore, the maximum values of boron contents of products and working solutions provided by EPIA are assumed even for the typical approaches, as the use of the maximum concentration product cannot be assumed to occur in rare cases.

The worst case level is expected to also cover uncertainty on possible higher boron concentrations in future formulations of liquid concentrates or products. Referring to this uncertainty, EPIA stated that the highest boron level attainable for any photographic (aqueous) solution would be 1.1% and recommended to consider 1% B as a maximum possible concentration for photographic solutions, as it is unlikely that the various components could all be dissolved (or dissolved within a reasonable timescale). This recommendation has been accepted for liquid film developer and fixer concentrates (Application of 1% B as RWC for Scenarios A1 and C1).

According to the available instruction leaflets of boron containing photochemicals, "1+4" diluted solutions (1 part concentrate + 4 parts water) represent generally the highest recommended concentrations of applicable working solutions. Using a maximum B concentration of 1% (see prior statement) a B-concentration of 0.2% can be calculated for the diluted solutions (disregarding that the concentrates and water do not exactly reveal the same densities). As no relevant differences in the boron content between working solutions made from liquid concentrates and powder formulations are expected, 0.2% B is considered to be also in the upper concentration range of working solutions made from powder formulations (Application of 0.2% B as RWC-concentration for Scenarios C2, D2 and C3, D3 (fixers), if no other information were available).

According to industry (EPIA 2009c, I&P 2010a), there is no practical advantage to a level above the concentrations of 0.17% for diluted film developer solutions made from liquid concentrates (Scenarios A2 and A3) respectively 0.23% for prepared film developer solutions made from powder formulations (Scenarios: B2 and B3). A value of 0.12% boron was originally indicated in the filled-in questionnaire as maximum value in the case of film developer preparation from powder formulations. As formulae for solutions with higher levels have been published by consumers, 0.23% was recommended as worst-case level by I&P Europe (2010a). As this argumentation has been accepted and 0.17% and 0.23% also correlate with the assumption, that the maximum boron concentration should be in the range of 0.2% B, these values are considered in the RWC approaches of these scenarios.

Table XX: Boron concentration of film developers: Liquid concentrates- Scenario A

Boron-concentration of liquid concentrates as supplied:	Typical:0.46 Maximum: 0.85	% w/w boron % w/w boron
Boron-concentration of prepared solution intended for use:	Typical: 0.09 Maximum: 0.17	% w/w boron % w/w boron

Table XXI: Boron concentration of film developers: Powder formulations- Scenario B

Boron-concentration of product as supplied:	Typical:0.32 Maximum: 5.5	% w/w boron % w/w boron
Boron-concentration of prepared solution intended for use:	Typical: 0.03 Maximum: 0.12	% w/w boron % w/w boron

Table XXII: Boron concentration of fixers: Liquid concentrates*- Scenario C

Boron-concentration of liquid concentrates as supplied:	Typical:0.46 Maximum: 0.46	% w/w boron % w/w boron
Boron-concentration of prepared solution intended for use:	Typical: 0.09 Maximum: 0.09	% w/w boron % w/w boron

*application either for film and paper processing

Table XXIII: Boron concentration of fixers: Powder formulations*- Scenario D

Boron-concentration of liquid concentrates as supplied:	Typical:0.18 Maximum: 0.18	% w/w boron % w/w boron
Boron-concentration of prepared solution intended for use:	Typical: 0.03 Maximum: 0.03	% w/w boron % w/w boron

*application either for film or paper processing

5.2.4 Estimation of contaminated surface area of skin during single tasks

No studies, models or recommended default values (e.g. exposure rate) were available for estimating exposure levels resulting from the derived exposure scenarios. Skill, experience and hygiene can differ significantly among consumers, therefore, the applied surface area of contaminated skin via the presented scenarios are intended to be conservative and to cover this uncertainty and variation. If the applier reveals skill and experience, the resulting exposure levels and the size of the contaminated surface area are expected to be significantly lower as the determined exposure levels. In this case, the assumed size of contaminated skin is expected to represent a significant overestimation for most cases.

On the other hand, it needs to be stressed that the exposure scenarios should cover all potential appliers, which includes unskilled handling of unexperienced persons of the general public.

Discussion of the applied values

Referring to the scenarios covering the pouring of liquids (A1, A2, B2, C1, C2, D2), the assumed exposed surface area of skin is expected to be generally an overestimation of the average exposure level, as it is unlikely that the total surface area of one hand is exposed each time during one event of pouring liquid. Spillages will usually be limited to smaller areas than assumed (total surface area of one or two hands).

Scenarios A3 and B3 “Development of films in trays” consider total dermal exposure of one hand respectively two half hands (420 cm^2) for the typical case and of two hands for the RWC-approach. It might be the case that the typical hobby photographer uses only his fingertips for moving the films in the tray. However, films have to be moved continuously up to ~ 20 minutes. Therefore, it cannot be excluded that the hands are occasionally immersed more deeply into the solutions and due to spillages, significant larger areas than the surface area of the fingertips/fingers might remain continuously wet during this activity. The assumption of the size of the surface area (420 cm^2) applied for these scenarios seems to be justified.

5.2.5 Exposure during handling of powder formulations (Scenarios B1 and D1)

No studies, models or recommended default values (e.g. exposure rates) were available for estimating exposure levels resulting from handling of powders by non-professionals.

For dermal exposure, industry recommended dust concentrations on skin of 0.1 mg/cm^2/d (typical) and 0.2 mg/cm^2/d (RWC). For inhalation exposure, industry recommended dust concentrations of 10 and 20 mg/m^3 air as typical and maximum concentrations, based on data published by Woskie et al (1994). However, these latter data reflect the occupational environment, which differs from the expected exposure scenarios of consumers. Additionally, the recommended values are rather vague estimates and do not represent the mean or the highest value measured, but rather are 75th percentile values from the values reported by Woskie et al. (1994).

Exposure calculations were therefore based on estimates provided by EASE (EUSES 2.1) (see section 3.2.3) which do not refer to this particular scenario, but to occupational settings based on measured values from a diverse range of activities. This is considered to reflect and cover the present exposure situation best without any further data for refinement. The maximum values of the calculated EASE-values were applied for the RWC-approach (dermal 0.1 mg/cm^2/d, inhalation 50 mg/m^3) and the arithmetic mean of the range for the typical approach (dermal 0.05 mg/cm^2/d, inhalation 27.5 mg/m^3).

Ventilation conditions at industrial workplaces are expected to be better than in consumer settings, considering that powder handling by consumers is performed indoors, possibly in small rooms with little or no ventilation. The applied EASE-values may lead to an underestimation of consumer exposure. On the other hand, the amounts of product handled, release times and resuspension of settled dusts are expected to be much higher in industrial workplaces, which would lead to overestimation of consumer exposure. As variation of the exposure rates is expected to be high depending also on the skill and hygiene of the operator and on the properties of the product (e.g. particle size distribution), uncertainty and variation are estimated to be high.

27.5 and 50 mg/m^3 seem to be comparatively conservative estimates for dust concentrations in air during pouring of these powders (one package per day à 570 g). Based on the described properties of the powder formulations it is assumed that particles will settle rapidly (This assumption is not validated by measurements or by representative particle size distributions of the products). Therefore, the duration of exposure is estimated to last 15 minutes as no details for a refinement were avaiable. Further, it is assumed that consumers generally keep distance from the powder, during the short peaks of dust exposure. Spending 15 minutes at air concentrations of 27.5 and 50 mg/m^3 is expected to be a conservative approach.

EPIA and EASE estimates are based on data which refer to working rooms with some kind of ventilation, which cannot be expected, for the present scenarios. They might therefore underestimate concentrations, if the developer is mixed in an unventilated darkroom. No model or measured data on consumer dust exposure in an unventilated room were available. Rough estimates of inhalation exposures under unventilated conditions are given at the end of this document, which are intended to give a notion on the range of possible exposures for these uncertain conditions (See Annex IV).

5.2.6 Frequency and duration of tasks

Estimates of the frequency and duration of tasks referring to the handling of the liquid concentrates and powder formulations as supplied (Scenarios A1, B1, C1, D1) were provided by EPIA and I&P Europe. It is assumed that consumers of these products produce sufficient solution to allow several respectively all the planned events of photographic processing on a single day. The number of events of preparing solutions should be generally not higher than one event per day (EPIA 2009a). Based on this statement the applied frequency of one event per day for the typical scenario seems to be realistic, and 2 events per day have been applied in the RWC scenarios to cover remaining uncertainty of task frequency.

Frequency and duration of the preparation of solutions and film development in tanks respectively in trays (Scenario A2, A3, B2, B3, C2, C3, D2, D3) are personal estimates relying on information from safety data sheets, literature and experience of appliers (expert judgement, screening of discussion forums in the internet). The combined scenarios A1+A2+A3, B1+B2+B3, etc. are

intended to comply with several hours of photographic processing per day (estimate: duration of the combined scenarios: typical: ~3 hours, RWC: ~5 hours). As the variability and the preferences among appliers might differ significantly, several short lasting events of photographic processing per week respectively single events of long lasting activities per month are also likely and conceivable. The assumed frequency and duration of tasks are considered to cover the likely use pattern of consumers. If some operators intended to frequently perform higher numbers of cycles respectively to develop more films than estimated for this assessment, it is likely that this is done using larger tanks containing more films, respectively that the user is supported by automatic processing for efficient handling of the films. This would probably result in less or at least similar exposure levels as for the derived scenarios.

The assumed developing times for preparation of films in trays (10min respectively 20min, Scenarios A3, B3, C3, D3) rely on values from several instruction leaflets of different manufacturers and suppliers (Kodak 2007, Ilford 2004, etc.) which are intended as recommendations for the users. They are expected to be representative to estimate typical and maximum values.

6 DISCUSSION OF RESULTS

The RCRs are derived using a General Population-DNEL long term, systemic of 0.096 mg B/kg bw/day for developmental effects. This DNEL was derived using the study with the lowest NOAEL (9.6 mg B/kg bw/day) from an oral developmental study fulfilling the information requirements to evaluate developmental effects (OECD 414, GLP). With regard to developmental effects a single peak exposure can be sufficient to induce effects on the developing foetus when occurring in the appropriate time window of development. For effects on fertility a DNEL of 0.175 mg B/kg bw/day was derived. Effects on fertility are covered by the lower DNEL for developmental effects.

Scenario A and B cover the use of film developers. Scenario C and D refer to the use of fixers for film respectively paper processing (see section 3.2.1). They contain the tasks „preparation of working solutions" and "their application for tank respectively tray processing". The development of plane films in trays is time consuming and complex (Scenario A3, B3, C3, D3), therefore, this procedure is much less widespread among consumers than the development of films in tanks (Scenario A2, B2, C2, D2) and tray processing of papers (C4, D4). Therefore, combination of scenarios A1+A2, B1+B2, C1+C2+C4 and D1+D2+D4 covering only "preparation of working solutions", "tank processing" and "tray processing of papers" (only relevant for fixers) are expected to comply with the common use pattern of most consumers.

As it cannot be excluded that an operator, who develops films in trays, additionally prepares films in tanks, it is possible that all three scenarios A1+A2+A3 or B1+B2+B3 are performed on the same day, even if the probability of this scenario combination is expected to be low (the probability of this case is unknown). The derived RCRs for this combined scenario are determined to be 0.08 (typ.) and 0.22 (RWC) for Scenario A and 0.13 (typ.) and 0.78 (RWC) for Scenario B, if excluding boron exposure from other sources (see table XVI). These RCRs are below one, but already quite close to one when regarding the RWC-values. Based on the calculations in the present evaluation, these scenarios represent a significant source of exposure.

The RCRs of the combined scenarios referring to the use of fixers are comparable to the combined scenarios for film developers for the typical and RWC approaches (see tables XV and XVI). Therefore and as the same models and similar assumptions were applied, film developers and fixers are discussed together. The RCRs of the combined scenarios are not summed up with the RCRs of other photographic products (e.g. film developer (liquid concentrate) + fixer (powder)), as it is unknown how likely it is, that a consumer uses two or more boron containing photochemicals. There are only a few boron containing products on the market.

It needs to be stressed that the typical approach is also intended to be conservative and to cover risk based on data provided by industry (boron concentration of currently supplied products and recommended dilutions of working solutions). As the use pattern, skill, experience, hygiene of

consumers and the boron content of products and working solutions can differ significantly and are also partially unknown, the variation and uncertainty of these input parameters were encountered using conservative estimates, resulting in high RCRs for the RWC-approach. The RCRs of the RWC-approaches describe the risk, resulting from the assumption that all applied parameters are as disadvantageous as conceivable. Therefore, these scenarios seem to be unlikely to occur, but indicate also the impact of the parameters and the possible range due to uncertainties and variation.

Furthermore, the high RCRs result partially from the assumption of no use of PPE. Considering use of personal protective PPE e.g. gloves, tweezers is not justified for this assessment as this is not the general way of estimating consumer exposure (in line with ECHA guidance on IR and CSA, Chapter R15), even if it is recommended by the manufacturer. The reason is, that it can not be excluded that operators waive the use of PPE due to comfort and unawareness of the risk. In the present case, screening of internet forums revealed that some operators use their bare hands during all tasks, also for tray development of films, resulting in an intense and continuous contact with the diluted solutions.

The presented exposure scenarios and exposure levels are expected to cover foreseeable use and exposure of consumers. Nevertheless, underestimation of exposure levels is possible when considering the uncertainty of the derived dermal exposure values. The current value for percent absorption is rather low (0.5%) and the data supporting this value are not very robust. Though in a total weight of evidence it was concluded that dermal absorption of boron compounds through intact skin is low, higher values than 0.5% are conceivable. If the dermal absorption would e.g. be doubled, the dermal exposure levels of the referring scenarios would also be doubled. The resulting total exposure via the combined scenarios and RCRs would be considerably increased. Moreover, it has to be noted that boron absorption through damaged skin is significantly higher.

The combination of the photographic application scenarios and the background exposure levels via food and drinking water suggest that RCR's below 1 are expected for most combined exposure scenarios (see table XVIII and XIX). Only for the worst-case exposure level in the combined Scenarios B1+B2 and B1+B2+B3 the RCR values will be above 1 when combined with typical and RWC background exposures, suggesting a potentially unacceptable risk (combined RCRs of 1.17 and 1.26, with a contribution of 0.48 from typical food and drinking water exposure, and combined RCRs of 1.38 and 1.47, with a contribution of 0.69 from RWC food and drinking water exposure).

As possible occupational and consumer exposures are not included in this calculation but could contribute with significant amounts to the total boron exposure it can be anticipated that the RCRs of the derived scenarios could be considerably higher. Further, a broad variability with regard to nutritional boron uptake must be assumed, considering vegetarians and people consuming mineral waters with rather high boron concentrations (depending on the geochemical origin). Another source could be nutrition supplements which can result in boron uptake as high as 1-10 mg/day. Risk for human health is possible considering cumulative exposure based on several potential sources. Photographic applications might lead to a significant contribution to the boron uptake on single days when photochemicals are applied.

The present evaluation relies on conservative assumptions due to uncertainties and data gaps. This means that more information and a refinement of the derived conditions would help to achieve more realistic estimates. Refinement is mainly conceivable with regard to improving the knowledge on the exposure levels expected for consumers. It would be important to have data on airborne dust concentration which can be expected when consumers are applying boron containing photochemicals (e.g. particle size distributions of products, measurements of comparable tasks - consumers, small rooms, no ventilation). With regard to exposure to liquids the possibilities for refinements are minor as the boron content of the working solutions cannot be reduced without affecting its utility.

Another factor that could help to refine the assessment is the recommended reevaluation of the derived values for dermal absorption. It could further be considered to carry out another in vitro

test using finite as well as infinite dosing. This might not lead to big changes in the derived values but would increase the reliability of the values.

Further, a refinement of the default assessment factors for DNEL derivation seems possible when new information on toxicokinetic behavior in rats becomes available and a detailed evaluation of the complete available toxicokinetic database is carried out.

7 SUMMARY OF RESULTS AND CONCLUSION

Summary of results

For all typical and reasonable worst case scenarios for consumer applications of photochemicals RCRs are below 1. This holds true when each scenario is regarded on its own and when the use of only one boron containing photochemical product is considered per day (see tables XV and XVI). RCRs of combined typical consumer exposures are also below 1 when added to typical or RWC background exposure levels via food and drinking water (see tables XVIII and XIX).

RCRs above 1 are reached when typical and RWC background exposures are combined with consumer RWC exposure scenario B. The combination of RWC-scenarios of the single scenarios A, C, or D including typical and RWC background exposure would lead to RCRs below 1, although already quite close to 1 for the RWC values.

The combination of background exposures with combinations of RWC scenarios of A, C, and D would result in RCRs above 1. However, the likelihood that several boron containing photographic chemicals, e.g. film developer and fixer, are used on the same day is unknown as there are only a few boron containing products on the market.

It is to be noted that many of the applied approaches in the present evaluation rely on conservative assumptions due to uncertainties and data gaps. The conservatism applied could be replaced by a refined assessment, if adequate information and time was available.

At the present stage, risk management measures (RMM) should be considered in order to improve exposure determinants of the RWC scenarios. These could be the requirement to only supply the general public with products in the form of granulated powder, the substitution of powder formulations by liquid formulations or alternatively to introduce a concentration limit for the use of boron compounds supplied in powder products.

Possible risk management measures

As indicated above, at the present stage risk management measures (RMM) should be considered in order to achieve acceptable control of risks for specific amateur uses of photochemicals. The only scenarios, for which not adequately controlled risks were identified in the present evaluation, were those in which powder formulations of film developers were applied (considering boron exposure via diet and drinking water).

Possible measures to reduce the risk could be the substitution of powder formulations by liquid formulations or the requirement to only supply the general public with products in the form of granulated powder. It has to be noted that feasibility and effectiveness of this measure to reduce boron exposure of consumers was not evaluated for the present assessment. A replacement by boron-free products seems possible and should therefore be considered as another option.

The products containing film developers in powder form are currently the only photographic consumer products with boron concentrations exceeding the specific concentration limit of 1% boron (this equals e.g. 5.5% boric acid) for classification and labelling of mixtures as toxic to reproduction (Category 2, R60, 61). Labelling of products can be regarded as a RMM, but as for the application of PPE, it cannot be guaranteed that the labelling of a product triggers the appropriate behaviour of the consumer.

The introduction of a concentration limit for the use of boron compounds supplied in powder products would be another RMM option.

Conclusion

RAC concludes that the use of boric acid and borates in photographic applications in itself does not pose a risk to consumers. However, as there are more possible sources that contribute to the total boron exposure of consumers, these additional sources have to be considered in the risk assessment of boron compounds.

Food and drinking water represent a significant source of exposure to which the general public is exposed on a daily basis. When data on exposure through diet and drinking water is applied as estimated by Austria (2009) an RCR above 1 is obtained for the scenarios based on reasonable worst-case parameters in the specific case of consumers which may prepare solutions from powder formulations for film developers and use them for tank or tray processing of film on the same day.

The identified risk partly results from conservative assumptions due to data gaps with regard to use pattern, consumer behaviour and boron concentrations in future products and products of companies not covered by the information presented by EPIA and I&P. Further, it has to be noted that a detailed evaluation of the toxicokinetic data for boron compounds in rats and humans may result in a higher DNEL than applied for the present risk characterisation.

In contrast it has to be considered that other sources of boron exposure (like other boron-containing consumer products, or occupational exposure) were not considered in the present evaluation, but would further contribute to the total boron exposure, and thus to the risk for consumers.

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ANNEXES

Annex I: Overview on human health endpoints - summary of Austria (2009).

Annex II: Formula and calculation of the dermal absorption percentage according to Wester et al., 1998.

Annex III: ^{10}B content in the receptor fluid in the in vitro experiment by Wester et al. (1998).

Annex IV: Feasibility of exposure calculation for the dilution of a powder developer in an unventilated darkroom (comment on Scenarios B1 and D1)

ANNEX I: Overview on human health endpoints. Summary of Austria (2009).

Toxicokinetics					
- **Absorption**	Readily absorbed orally and by inhalation (with regard to respirable particles) Dermal absorption see section 2.4				
- **Distribution**	Rapidly and evenly distributed through body water With the exception of bone - no accumulation in tissues				
- **Metabolism**	Not metabolised Exists mainly as boric acid under physiological conditions				
- **Elimination**	Excreted almost exclusively in the urine, regardless of the route of administration; clearance is slightly higher in pregnant women compared to non-pregnant individuals; tubular reabsorption occurs in both. Half-life < 27.8 hours in humans Renal clearance is 3-4 times faster in rats compared to humans based on a body weight comparison				
Acute toxicity - **oral** - **dermal** - **inhalation**	The boron compounds under investigation are not classified for acute toxicity. Acute toxicity studies are available for boric acid, disodium tetraborate anhydrous, pentahydrate and decahydrate for oral, dermal and inhalation route. LD_{50}/LC_{50} values are far above the derived NOAELs for reproductive toxicity and the cut off values for classification, based on boron equivalents. For acute toxicity read across to boric oxide, orthoboric acid, sodium salt and tetraboron disodium heptaoxide, hydrate is possible on the basis of boron equivalents. Human poisoning cases occured after oral and inhalation exposure as well as after dermal exposure via damaged skin. In the literature, the human oral lethal dose is regularly quoted as 2-3 g boric acid for infants, 5-6 g boric acid for children and 15-30 g boric acid for adults. These data are largely unsubstantiated. In most cases it is difficult to make a good quantitative judgment particularly since medical intervention occurred in most cases and there were often other unrelated medical conditions (Culver and Hubbard, 1996). One recent case of an 18-month-old child who died following the accidental ingestion of a boric acid-containing, commercially available household pesticide against cockroaches, ants and flies (Hamilton, 2007) indicates that the toddler population is a vulnerable group. It has to be noted that powder pesticides contain up to 99% of boric acid. In the past there were several poisoning cases after medical treatment of burns and damaged skin with preparations containing boric acid (Kliegel, 1980). Such medical uses are now obsolete because of its low efficacy and comparatively high toxicity. No DNEL has to be derived for acute toxicity.				
Irritation/Corrosivity - **skin** - **eye** - **resp. tract**	NOAEC = 0.8mg B/m^3	NA	No AF needed (human data, NOEC, worker population)		NA

Skin irritation: The boron compounds under investigation are not classified as skin irritants. Boric acid, disodium pentahydrate and decahydrate were mildly irritant to abraded skin, but not irritant to intact skin (skin irritation studies on rabbits, according to approved guidelines, Austria, 2009).

Eye irritation: Disodium tetraborate anhydrous, pentahydrate and decahydrate fulfill the criteria for classification as eye irritant according to Annex VI, 67/548/EEC. Boric acid does not fulfill these criteria. When tetraborates, orthoboric acid, sodium salt and tetraboron disodium heptaoxide, hydrate are dissolved in aqueous solution this results in an alkaline pH. In contrast, boric acid leads to acidic conditions This can also be expected for boric oxide. The differences in pH in the eye lining liquid are probably the explanation for the different effects of boron compounds on the eye.

Respiratory irritation: The boron compounds under investigation are not classified as respiratory irritants. However, in Austria (2009) boron compounds were identified to act as sensory irritants based on effects observed in humans (EPA, 2004; Wegman et al. 1991; Garabrant 1984, 1985; Woskie et al., 1994, 1998; Cain et al., 2004, 2006) and by the results of an Alarie-test on mice (Krystofiak & Schaper, 1996). The acute irritant effects were observed in workers exposed to boric acid and tetraborates. Many of the irritant symptoms (sensory irritation of the nose and throat, cough, phlegm production and broncho-constriction - as evidenced by a decrease in forced expiratory volume in 1 sec (FEV1)) are part of the respiratory defense reflex, the function of which is to protect the body from inhaled irritants. This reflex can be triggered by agents that stimulate receptors in the respiratory tract e.g. on the trigeminal nerve (Wegman et al. 1991, Nielsen et al., 2007, Krystofiak & Schaper, 1996). In this respect osmolarity was discussed as an important factor next to pH changes in the liquid layer above the mucous membranes. The actual mechanism, however, has not yet been elucidated. The identified dose-descriptor for acute irritant effects is the NOEC value of 0.4 mg B/m^3 based on Wegman et al. (1991). The value has to be corrected by the factor 2 as the methods used for exposure measurements underestimated air concentrations. This results in a final NOEC of 0.8 mg B/m^3. For more details see Austria (2009).

Corrosivity: The boron compounds under investigation are not corrosive.

In Austria (2009) a Worker-DNEL acute, inhalation, local = 0.8mg B/m^3 was derived based on the NOEC of 0.8mg B/m^3 (Wegman et al., 1991). This value is on the lower end when comparing it to national and international recommendations for boron air concentrations in the occupational setting. The derived value was mentioned to be also protective against eye irritating properties of boron compounds.

Table A: International/national recommendations regarding boron (boric acid & borates) in air

Organisation	Standard	Remarks	Reference
BAuA, Germany, Europe	AGW: 0.5 mg boron/m^3 boric acid 2.6 mg/m^3, sodium-tetraborate anhydrous 2.1 mg/m^3, sodium-tetraborate pentahydrate 3.0 mg/m^3, sodium-tetraborate decahydrate 4.0 mg/m^3.	based on Wegman et al. 1994 and Culver et al. 1994	BAuA, 2007
ACGIH, USA	Borate compounds, inorganic (*) (borax, boric acid and sodium tetraborates) TLV (8-hour TWA): 2 mg/m^3 STEL (15 min TWA): 6mg/m^3		ACGIH, 2006
NIOSH, USA	Borax (*) REL TWA (10 hours): 5 mg/m^3		NIOSH, 2005

AGW Arbeitsplatzgrenzwert = Occupational Exposure Level; MRL = Minimal Risk Level, TWA Time Weighted Average; STEL Short Term Exposure Limit; TLV Threshold Limit Value; REL Recommended Exposure Limits.

(*) These values are not enforceable regulatory values and are only recommended exposure limits.

Sensitisation - **skin** - **resp. tract**	The boron compounds under investigation have no sensitising properties. Negative Buehler tests according to OECD 406 are available for boric acid, disodium tetraborate pentahydrate and disodium tetraborate decahydrate (Austria, 2009). There are no indications from work place exposure that these compounds are respiratory sensitisers. No DNEL has to be derived for sensitisation.				
Repeated dose toxicity - **oral** - **dermal** - **inhalation**	A number of studies on boric acid or disodium tetraborate decahydrate in diet or drinking water for periods of 30 days to two years in rats, mice and dogs are available. Some of these studies do not comply with current standards and are not GLP conform. However, the majority of these studies confirm that the main target organ of boron toxicity is the testis. As all boron compounds are transformed to boric acid under physiological conditions these results can be translated to the other boron compounds under investigation. The repeated dose toxicity effect on the testis is covered by the section on reproductive toxicity.				
Mutagenicity	From several negative in vitro studies (OECD 471, 476, 473) and one in vivo study (OECD 474) on boric acid it can be concluded that the boron compounds under investigation have no mutagenic properties. No DNEL/DMEL has to be derived for mutagenicity.				
Carcinogenicity	Based on a 2-year mouse study following the NTP-protocol (NTP, 1987) boric acid is not carcinogenic. Further, several chronic toxicity studies on boric acid and disodium tetraborate decahydrate in rats and some low quality studies in dogs exist in which no indications for carcinogenic effects were observed. Another 2-year study in rats can be used to assess carcinogenic effects of boric acid and disodium tetraborate decahydrate. Only 10 animals/sex of the control and high-dose group were macroscopically and histologically examined, which limits the conclusions that can be derived from this study. Although not carried out according to modern standards, nor to GLP, it is well performed and reported. As all boron compounds are transformed to boric acid under physiological conditions these results can be translated to the other boron compounds under investigation. Based on the available data he boron compounds under investigation are judged non carcinogenic. No DNEL/DMEL has to be derived for carcinogenicity.				
Reproductive toxicity					
Fertility impairment - **oral** - **dermal** - **inhalation**	NA	$NOAEL_{effects\ on\ fertility}$ = 17.5mg B/kg bw/day	AF = 100 (interspecies – rat to human: 10; intraspecies: 10)	NA	$DNEL_{systemic}$ = 0.175mg B/kg bw/day*
	Fertility effects of boron compounds were investigated in several epidemiological studies in workers and populations living in areas with high environmental levels of boron. Truhaut et al., 1964, Tarasenko, 1973, Krasovskii et al., 1976, Whorton, 1994, Tuccar, 1998 and Sayli, 1998, 2001, 2003 were available at the time the Commission Working Group of Specialised Experts in the field of Reprotoxicity (Ispra, October 5-6, 2004) was held. They came to the conclusion that the epidemiological studies available at that time were of insufficient quality to demonstrate presence or absence of fertility				

	effects. A recent review, on studies carried out on Chinese boron mine workers (Scialli et al., 2009) was generated by an expert panel initiated by industry. It allows no final conclusion on effects of boron exposure on human fertility. Male infertility was observed in breeding studies in rats, mice, deer mice and dogs (Weir, 1966a, b, c, d, Fail et al., 1991, Dixon et al., 1979, Lee et al., 1978, Treinen & Chapin, 1991, Fail et al., 1989). The underlying cause for male infertility was identified to be testicular atrophy. A series of studies was published providing insight into the mechanistic nature of the lesions in rats. Good correlation between doses inducing spermatogenic arrest and infertility could be observed. The effects were reversible at lower doses, but no recovery occurred at doses causing germ cell loss. Germinal depletion correlated well with increased plasma levels of FSH. Levels of other hormones, like testosterone and LH were not always affected. A NOAEL of 17.5 mg B/kg bw/day in rats (Weir, 1966a,b,c,d) could be derived. Female fertility was affected as demonstrated by Fail et al. (1991) and Weir (1966c, d). The underlying mechanism is much less investigated than for effects on male fertility. Effects observed were infertility in female rats at 58.8mg B/kg bw/day (Weir, 1966c,d) and reduced fertility in female mice at 111.3mg B/kg bw/day (Fail et al. 1991). Fail et al. (1991) investigated different endpoints at different dose levels in a continuous breeding study according to the NTP protocol. The following effects in female mice were seen at the lowest dose at which these effects were investigated (LOAELs). F0 females had normal cyclicity, but revealed reduced average dam weight on post natal day 0, reduced average gestational period and their litters showed significantly reduced weight when adjusted for litter size (111.3mg B/kg bw/day). The last observation was also seen in litters from the F1 generation. In contrast to F0 females the oestrus cycle length was reduced in F1 females (26.6mg B/kg bw/day). Weir (1966c,d) described infertility of female rats at 58.8 mg B/kg bw/day when paired with untreated males (only 2 out of 16 matings produced litter). With regard to number of conceptions, number and size of litters, number of deaths, weight of pups at 24 hours and at weaning as well as cross signs of abnormalities no differences compared to control animals were recorded at 17.5 mg B/kg bw/day. A NOAEL of 17.5 mg B/kg bw/day could be derived.				
Developmental tox - **oral** - **dermal** - **inhalation**	NA	NOAEL = 9.6mg B/kg bw/day	**AF = 100** (interspecies: 10; intraspecies: 10)	NA	$DNEL_{systemic}$ = 0.096mg B/kg bw/day *
	With regard to developmental effects no human data exist. The available data from animal studies are sufficient to conclude that prenatal exposure to boron by the oral route can cause developmental toxicity. Developmental effects were seen in three different mammalian species, namely rat, mouse and rabbit, with the rat being most sensitive. From the most robust study in rats (Price et al., 1996) the lowest NOAEL = 9.6 mg B/kg bw/day can be derived. Reduced foetal body weight per litter and increased incidence in short rib XIII were seen at the LOAEL = 13.3 mg B/kg bw/day. In another rat study a LOAEL = 13.7 mg B/kg bw/day for skeletal effects (short rib XIII) was derived (Heindel et al., 1992). Other effects seen at maternally toxic doses were visceral malformations like enlarged ventricles and cardiovascular effects.				

Annex II: Formula and calculation of the dermal absorption percentage according to Wester et al., 1998.

A basic $^{11}B/^{10}B$ ratio for each volunteer was calculated from boron excretion on 4 consecutive pre-treatment days. For this purpose a weighted average of the basic ratio over that period was calculated.

- The amount of expected ^{10}B in µg (reflecting the ^{10}B amount resulting from dietary boron consumption) was calculated using total urine boron values, the basic $^{11}B/^{10}B$ ratio and the relative weight ratio of ^{11}B to ^{10}B.

The following formulas were used:
(1): TOTBORON = $^{10}B + ^{11}B$
(2): BASIC RATIO * (weight ^{11}B / weight ^{10}B) = ^{11}B / ^{10}B ➔
B11 = BASIC RATIO * (weight ^{11}B / weight ^{10}B) * ^{10}B ➔
(1) + (2): TOTBORON = ^{10}B + BASIC RATIO * (weight ^{11}B / weight ^{10}B) * ^{10}B ➔ divided by ^{10}B:
TOTBORON / ^{10}B = 1 + BASIC RATIO * (weight ^{11}B / weight ^{10}B) ➔
Change formula to:
^{10}B /TOTBORON = 1/ /(1 + BASIC RATIO * (weight ^{11}B / weight ^{10}B)) ➔
Multiplied by TOTBORON:
^{10}B = TOTBORON / (1 + BASIC RATIO * (weight ^{11}B / weight ^{10}B)) ➔
As this is the expected B10 the following formula can be derived:
^{10}B EXPECTED = TOTBORON / (1 + BASIC RATIO * (weight ^{11}B / weight ^{10}B))

- The amount of total ^{10}B excretion is calculated in a similar way: instead of the basic ratio the actually measured ration for each day is used – the following formula can be derived:

B10TOTAL = TOTBORON / (1 + Measured RATIO per day* (weight ^{11}B / weight ^{10}B))

- To calculate the Excess ^{10}B excreted ^{10}B EXPECTED was subtracted from ^{10}B TOTAL

B10EXCESS = ^{10}B TOTAL - ^{10}B EXPECTED

Figures 1 presents the calculated values for excess ^{10}B excreted during the whole period for the experiment. In figure 2 the same graph is shown including standard deviations.

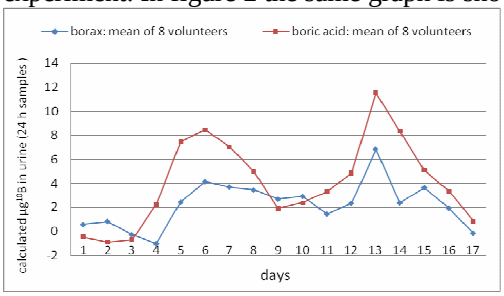

Figure 1

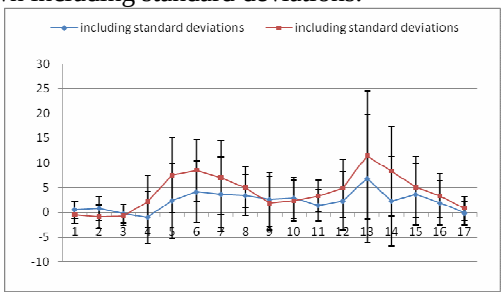

Figure 2

Annex III: ^{10}B content in the receptor fluid in the in vitro experiment by Wester et al. (1998).

Figure A shows the results for all 6 skins from the infinite experiment for 5% boric acid (1ml / 1cm^2). In figure B skin #4 was removed. The results of this skin showed a rather high variability among different test units (single exposure cells).

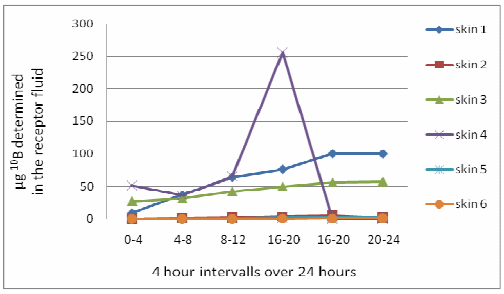

Figure A

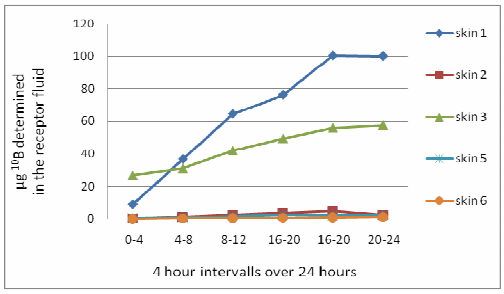

Figure B

Annex IV: **Feasibility of exposure calculation for the dilution of a powder developer in an unventilated darkroom (comment on Scenarios B1 and D1):**

Powder Developers are used for black and white film processing in spiral tanks, deep tanks dishes/trays or rotary processors. This processing has to be done in a room which can be completely blacked out. The user is advised to setup his darkroom first and to mix the chemicals and do the processing afterwards: "Whichever room you choose as your darkroom (kitchen, bathroom or cupboard), it needs to be completely blacked out to stop light from entering. For windows use thick card cut to shape and held in place with black canvas tape. For doors use tape or black cloth or canvas to seal the edges." (Ilford 2003) This means, that very small rooms may be chosen and that no ventilation can be expected during the whole process.

While pouring powder developer into water, dust may be released into air. (Granular and powder products of boric acid have a mean particle diameter range of <75 – 680µm, which clearly includes particle diameters for suspended and respirable particles (ECHA 2008a).) Exposure to this dust will continue during the whole process, if the darkroom is closed before dilution. Current databases for exposure assessment to dusts, like EASE or Models from the Technical Notes of Guidance for Human Exposure to Biocidal Products, are based on measured data under conditions which include a certain kind of ventilation, even if no LEV is provided. This means, that these models cannot be applied to developer use in an unventilated darkroom at home, because they may underestimate dust exposures.

Therefore, exposure to dust developers in unventilated darkrooms can only be calculated by very rough methods which are not able to give more than a notion about the range of exposure.

Exposure via inhalation

Assuming that released dust behaves like a volatile compound in the air, the equation from the ECETOCTRA tool Version 2 may be used for assessment of exposure via inhalation. It is based on tier 1 equations from the ECHA Guidance on IR and CSA Chapter R15, but it includes a factor for the fraction released into air. In reality, only a small amount of the developer powder will be released into air. This amount depends on mechanical handling conditions and particle diameters. Concentrations may be reduced in time due to particle deposition which depends on particle diameter, too. But as these conditions are not known, neither the released percentage nor the percentage reduced by deposition can be estimated. To illustrate the relationship between release fraction, dust concentration and Boron exposure, exposure is calculated for different orders of magnitude of the released fraction. The calculation is done with the following use conditions listed in table 1.

Table 1: Conditions of powder developer use

condition	Worst Case	Source	Typical Case	Source
Product **I**ngredient (g/g)	0.055	EPIA	0.055	EPIA
Amount Product Used per Application (g/event)	570	EPIA	120	EPIA
Fre**Q**uency of Use (events / day)	1	EPIA	1	EPIA
Exposure **T**ime (hr)	0.7	Maximal development time at 20°C for Microphen according Ilford 2004: 27 min, plus 15 min preparation time (EPIA)	0.5	typical development time at 20°C for Microphen according Ilford 2004: 15 min, plus 15 min preparation time (EPIA)
Inhalation **R**ate (m^3/hr)	1.42	AUH 1995 light activity, adult	1.08	AUH 1995 light activity, adult
Room **V**olume (m^3)	10	ConsExpo General Factsheet, bathroom	10	ConsExpo General Factsheet, bathroom
Body **W**eight (kg)	60	Standard default	60	Standard default

Table 2: Worst case consumer exposure to powder developer via inhalation with different fractions released to air

Product **I**ngredient (g/g)	**A**mount Product Used per Application (g/event)	**FreQ**uency of Use (events / day)	**F**raction Released to Air (g/g)	**E**xposure **T**ime (hr)	**I**nhalation **R**ate (m^3/hr)	**C**onversion **F**actor	Room **V**olume (m^3)	**B**ody **W**eight (kg)	**Exposure (mgB/kg /day)**	**Dust Concentration (mg/m³)**
(PI x	**A x**	**FQ x**	**F x**	**ET x**	**IR x**	**1000) /**	**(V x**	**BW)**		
0.055	570	1	1	0.7	1.42	1000	10	60	51.9365	57000
0.055	570	1	0.1	0.7	1.42	1000	10	60	5.19365	5700
0.055	570	1	0.01	0.7	1.42	1000	10	60	0.519365	570
0.055	570	1	0.001	0.7	1.42	1000	10	60	0.0519365	57
0.055	570	1	0.0001	0.7	1.42	1000	10	60	0.00519365	5.7

Table 3: Typical consumer exposure to powder developer via inhalation with different fractions released to air

Product **I**ngredient (g/g)	**A**mount Product Used per Application (g/event)	**FreQ**uency of Use (events / day)	**F**raction Released to Air (g/g)	**E**xposure **T**ime (hr)	**I**nhalation **R**ate (m^3/hr)	**C**onversion **F**actor	Room **V**olume (m^3)	**B**ody **W**eight (kg)	**Exposure (mg/kg/day)**	**Dust Concentration (mg/m³)**
(PI x	**A x**	**FQ x**	**F x**	**ET x**	**IR x**	**1000) /**	**(V x**	**BW)**		
0.055	120	1	1	0.5	1.08	1000	10	60	5.94	12000
0.055	120	1	0.1	0.5	1.08	1000	10	60	0.594	1200
0.055	120	1	0.01	0.5	1.08	1000	10	60	0.0594	120
0.055	120	1	0.001	0.5	1.08	1000	10	60	0.00594	12
0.055	120	1	0.0001	0.5	1.08	1000	10	60	0.000594	1,2

Exposure under typical conditions would be below 0.06 mg B/kg/day, if the released fraction was below 1%. As this exposure would derive from a very high dust concentration of 120 mg/m³, it seems unlikely that a consumer would expose himself to it for half an hour.

Exposure under worst case conditions will be below 0.052mg B/kg/day, if the released fraction is below 0.1%. This exposure would derive from a dust concentration of 57mg/m³.

Dermal exposure:

Dermal exposure will result from contact to particles suspended in the air, from dust deposition from the air and from direct contact to powders and coarse dusts.

According to ECHA Guidance on IR and CSA Chapter R15, exposure from a non-volatile substance in a volatile medium might be calculated for tier 1 purposes, assuming that the substance contained in a thin layer over the skin contact area is fully absorbed. Applying this concept in a tier 1 calculation, no absorption factor should be applied together with the thin layer. Table 4 shows that according to this concept, exposure from suspended particles would be negligible, even with the highest calculated dust concentration of Table 1:

Table 4: Worst case dermal exposure to suspended particles from powder developer

Product **I**ngredient (g/g)	**Dust Concen-tration (mg/m³)**	**C**ontact **A**rea (cm^2)	**Fre****Q**uency of use (events / day)	**T**hickness of **L**ayer (cm)	**Conver-sion Factor m³ to cm³**	**B**ody **W**eight (kg)	**Exposure (mg/kg/day)**
(PI x	**CD x**	**CA x**	**FQ x**	**TL x**	**F**	**/ BW**	
0.055	57000	2082.5	1	0.01	0.000001	60	0.00108811

Even so, dermal exposure from dust deposition cannot be calculated due to the manifold influences on this process and the lack of information on particle diameters.

But if the release fraction is low, dermal exposure might derive mainly from direct contact with powders and coarse dusts, which does not depend as much from ventilation as dermal exposure from suspended and deposited particles. Therefore, for exposure from direct contact, calculation models from EASE based on measured data in workplaces without LEV might be an approximation.

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