Risk Assessment and Risk Management of Phthalates Revisited

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EXECUTIVE SUMMARY

1. Phthalates are a group of related compounds that are very widely used as plasticizers and solvents. They have been in use for about 75 years and can be found in a great variety of products including building materials, personal care products, toys and medical devices.

2. Originally, the two phthalates of most concern were DEHP in medical devices and DINP in toys. Expert panel reports that evaluated such exposures concluded that the risks were low although additional data would be useful in addressing remaining uncertainties. At about this time, the focus of concern shifted and broadened to possible adverse effects on the reproductive and developmental potential of infants and children exposed to a number of phthalates in plastics.

3. During the past decade governments and agencies in Europe and the U.S. have taken or proposed regulatory actions to limit exposures to phthalates in toys and other plastics to which infants and children may be exposed. The phthalates that have been the subjects of these actions are DnOP, DIDP, DINP, BBP, DBP, and DEHP.

4. While these actions were under consideration, a variety of expert panels met in Europe and the U.S. to carefully evaluate the exposures to and toxicities of the individual phthalates of most concern. These assessments have continued to the current date and have incorporated a large body of new research performed in the past decade.

5. As a result of new data, especially from biomonitoring studies, and expert re-evaluations, estimates of exposure of infants and children, especially from plastics, have decreased significantly.

6. While a variety of laboratory animal studies have been performed to fill data gaps, these new data have not resulted in significant changes in conclusions about the possible toxicity of phthalates.

7. Although there have been a number of epidemiological studies of possible adverse effects of phthalates, especially on male reproduction, the results have been inconclusive and/or contradictory. Thus, this research has not resolved uncertainties about the toxicity of phthalates to humans.

8. Based on the most recent exposure and toxicity data, including epidemiological study results, it can be concluded that human exposures to the phthalates of most concern are generally thousands of times lower than the lowest adverse effect levels for these phthalates in the most sensitive animal species.

9. Thus, re-evaluating the risk from phthalates leads to the same conclusions that were drawn almost a decade ago: (1) as currently used, phthalates do not pose a significant risk to the general public, including infants and children; and (2) there is no human evidence of adverse effects in the adults and children heavily exposed to phthalates due to leaching from medical devices, such

as tubing, used during intensive treatment procedures.

10. Since the evidence indicates that phthalates do not pose a significant risk to humans, current and proposed regulations to limit phthalate exposure are unlikely to be of any benefit to public health.

Introduction

The term phthalates, or phthalate esters, refers to a large group of compounds that share basic chemical similarities. However, the individual members of the group have unique physical and chemical properties and studies to date suggest that they also affect biological organisms differently. Although some of these differences in toxicity among phthalates are well established, at least in experimental animals, the data gathered to date are not sufficient to clearly elucidate the range of toxicological differences among phthalates, even among those most intensively researched.

Although studies on the toxicology of phthalates have been performed since they were introduced into commerce about 75 years ago, concern about their possible adverse effects in humans has been much more recent. These concerns date back about 25 years and were originally focused largely on one phthalate, diethylhexyl phthalate (DEHP), which was shown to cause cancer in rodents after very high lifetime exposures (NTP, 1982). In the 1990s, attention turned to the effects of DEHP on adults who were exposed to this compound through intensive medical procedures, such as dialysis. In addition, over the course of the next decade as public concern about the possible effects of environmental contaminants on infants and children grew,

the possible reproductive and/or developmental toxicity of di-isononyl phthalate (DINP), found in products to which this sub-population is often exposed, such as plastic toys, drew increased attention.

In the U.S., a number of expert groups were convened towards the end of the 20th century to carefully evaluate the toxicity of a number of phthalates and to assess whether or not humans of any age were at risk. One, an expert panel, brought together in 1999 by the American Council on Science and Health (ACSH) and chaired by former U.S. Surgeon General C. Everett Koop, critically evaluated the evidence on the possible risks associated with DEHP in medical devices and DINP in products used by infants and children (Koop et al., 1999). Another, a scientific panel, convened by the NTP Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR), met from 1998 to 2000 and examined the toxicology and risks associated with seven different phthalates - DEHP, DINP, dibutyl phthalate (DBP), butylbenzyl phthalate (BBP), diisododecyl phthalate (DIDP), di-n-octyl Phthalate (DnOP), and di-n-hexyl phthalate (DnHP) (Kavlock, 2002 a,b,c,d,e,f,g). Last, at about the same time, the International Agency for Research on Cancer (IARC) reevaluated its conclusions about the possible carcinogenicity of DEHP in humans (IARC, 2000).

The conclusions of the Koop panel were that "...DINP in toys is not harmful for children in the normal use of these toys" and that "DEHP, as used in medical devices, is not harmful to humans...". The conclusions of the CERHR panel distinguished among the phthalates assessed. According to the panel the scientific evidence suggested "negligible concern" about possible

human risks from DnOP exposures, “minimal concern” about possible human risks from DINP, DIDP, and BBP, “some concern” about some possible risks from DBP, and varied levels of concern associated with possible human risks from DEHP ranging from “minimal concern” for the general public to “serious concern” about critically ill neonates. IARC concluded that its original designation of DEHP as “possibly carcinogenic to humans”, which was based entirely on animal studies, should be changed to “cannot be classified as to its carcinogenicity in humans”, based on additional evidence on its mechanism of action (IARC, 1982; IARC, 2000).

In addition to its conclusions about risks, the CERHR panel identified a number of data gaps and made suggestions as to what additional research on both exposure and toxicity would be helpful in making more confident assessments of the risks of phthalates to humans (Kavlock, 2002c). In light of IARC’s conclusions that carcinogenicity was not a concern, the panels focused their requests for additional data on possible reproductive and developmental toxicities of phthalates. This article will assess the impact of the data that have been collected since this time. It will review the evaluations of these findings by experts in toxicology and epidemiology who have either published in the peer reviewed literature or have served on expert panels brought together by governmental organizations, particularly by the European Commission (EC).

Reports evaluating one or more phthalates have been issued by a number of EC organizations including the Scientific Committee on Consumer Products (SCCP), the Scientific Committee on Health and Environmental Risks (SCHER), the European Food Safety Authority (EFSA) (EFSA, 2005 a,b,c,d,e,f), the Scientific Committee on Emerging and Newly-Identified Health Risks

(SCENIHR) (SCENIHR, 2008), the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) (CSTEE, 2001 a,b,c, 2004) and the European Chemicals Bureau (ECB) (ECB, 2003 a,b,c, 2007). In addition, in 2005, the NTP-CERHR issued an update of its original report on DEHP (NTP, 2005). More recently, the Australian government issued a series of phthalate hazard assessments (NICNAS, 2008 a,b,c,d,e,f). These reports, together with recent research and review articles, provide the basis for this comprehensive overview of the data on phthalate exposure and toxicity developed during the past seven or eight years.

While the research and evaluations were taking place, a number of regulatory actions aimed at limiting exposures to various phthalates were enacted and/or proposed in both the European Union and in individual states in the U.S. as well as in the U.S. Congress (European Parliament, 2005; State of California, 2007; State of Maryland, 2007; State of Minnesota, 2008; U.S. Senate, 2008). Although some have addressed phthalates in cosmetics (European Parliament, 2004), the regulatory actions that received the most attention were focused on exposures of infants and children to plastic objects, particularly those that are often mouthed, such as toys. Most of these actions or proposed actions, whether in the U.S. or Europe, are quite similar and their provisions can be broadly characterized as follows. They forbid the marketing of: (1) DINP, DIDP and DnOP, at concentrations above 0.1% by mass of the plasticized material, in toys and childcare articles that can be mouthed; and (2) DEHP, DBP, and BBP, at concentrations above 0.1% by mass of the plasticized material, in toys and childcare articles. While Health Canada proposed regulations in 2007 aimed at the same types of phthalate exposures, it decided that the risk of only one phthalate, DEHP, warranted regulation (Health Canada, 2007). In light of these

actions, this article will focus on the six phthalates that have been characterized as posing a sufficient risk to warrant regulation. In addition to examining phthalate research and expert evaluations of the risks of these compounds, the implications of these regulations on public health will also be addressed.

The approach taken in this article is to first examine the issues related to phthalate exposure assessment including a discussion of the strengths and limitations of each assessment methodology currently in use. Following this, the approaches used for toxicity assessment of phthalates are described and discussed. A focus of this analysis is the meaning of the toxicity values that are generally used to characterize the potential adverse outcomes from exposure to phthalates. This discussion leads into a risk characterization section that examines the exposure and toxicity data for each phthalate individually and provides an overall assessment of what these data imply for the risk of each. This is followed by a section addressing whether the proposed or enacted risk management regulations are likely to have a positive impact on this risk and thus on public health.

Exposure Assessment

Sources

There are a large number of sources of phthalates, most of which reflect their use as plasticizers for Polyvinyl Chloride (PVC). These compounds are particularly useful in the production of soft PVC products such as plastic tubing, gloves, bags and toys. In addition, phthalates are found in building materials, home improvement products, personal care products and a variety of other

consumer products. Because phthalates may leach from plastics, some uses, such as in plastics used in food processing, have resulted in the presence of phthalates in foods. In addition to leaching of phthalate into food, other sources of exposure include release of phthalates into the air from building materials and skin contact with phthalate-containing personal care products. In evaluating exposure, particular attention has been paid to an uncommon route of ingestion exposure for environmental chemicals, mouthing (by infants and young children) of phthalates that leach out of plastic toys and other childcare products. Thus, multiple routes of phthalate exposure, including ingestion, inhalation, and skin contact, must be considered in any exposure assessment. The combination of wide use and multiple routes of exposure have led to detectable levels of phthalates in humans of all age groups.

Magnitude and time course

Two methods have been used for assessing overall human exposure to phthalates. One is modeling of exposures based on environmental phthalate measurements and behavioral assessments. The second is biomonitoring of phthalate or phthalate metabolite levels in human fluids and calculating exposures based on these analyses.

Modeling exposures using data from environmental analysis and behaviors

The modeling approach is carried out by combining information on the levels of phthalates in the environment; e.g., food, toys, consumer products, air, water, etc. with quantitative assessments of human behaviors; e.g., the amount of food ingested, the duration and characteristics of toy behavior, etc. to arrive at the total exposure to a particular phthalate through all routes of

exposure. The accuracy of such a number depends upon knowledge of: (1) all significant sources of each phthalate; (2) the concentrations of each phthalate in each of the sources and how these levels vary over time and location; and (3) behaviors, such as amount of food of each type ingested and frequency of ingestion. Because of the difficulty of collecting such data on phthalates from the multiplicity of possible sources, uncertainties in exposure values derived from this methodology are significant. In addition, because phthalates are so ubiquitous, contamination of samples from environmental sources can be a serious problem and lead to overestimates of exposures. While these difficulties should be kept it mind, the modeling approach does have the advantage of providing data for all age groups on the apportionment of exposure among sources and on the timing and duration of exposures - information that is generally not available from biomonitoring.

A type of ingestion exposure that is not usually considered in exposure assessment, namely mouthing, is one that has become critical for phthalates because of the concern about exposures of infants and toddlers through leaching of phthalates from plastic objects; e.g., soft plastic toys and teethers. In the absence of established protocols for making mouthing estimates, data have been gathered and assessed differently by various analysts resulting in large variations in estimates of the magnitudes of mouthing exposures. In some cases investigators have used worst case scenarios in making estimates although these are likely to significantly overestimate mouthing exposures (ECB, 2003b).

Results from the modeling approach suggest that the daily variability in exposure is significant and can be as high as two to three orders of magnitude (Wormuth et al., 2006). Considering this

high variability, those performing the modeling must decide on the most appropriate metric for the inputs into the exposure assessment; i.e., environmental measurements and behavioral assumptions. Different investigators have chosen different metrics; e.g., 90^{th} percentile, 95^{th} percentile, worst case, etc. resulting in a substantial range of exposure estimates. The more the metric reflects the extreme values of each input parameter, the more likely that the resulting exposure value will significantly overestimate the real exposure. In general, expert panels have chosen high but not extreme metrics so that the exposure values selected are conservative and provide a margin of safety. As indicated in the subsequent discussions of the specific phthalates, more extreme input values have been chosen by some groups (CSTEE, 2001a).

In addition to the potential for producing exaggerated exposure values by selecting extreme metrics, modeling can lead to potentially misleading results when the average daily exposures are heavily influenced by infrequent but high magnitude exposures to specific sources. As an example, averaging exposures over the whole year from the use of spray paints just a few times a year leads to the conclusion that they contribute significantly to DINP and BBP exposures in some age groups (Wormuth et al., 2006). Since toxicity often depends on both the magnitude and the time course of exposure, such average daily values may not be the best numbers to compare to the results of toxicity studies in which animals are exposed to constant daily doses.

Modeling has been used to assess the relative contributions of various routes of exposure as well as the absolute magnitude of exposure for each phthalate in each population. Because of the issues related to mouthing and also the lack of comprehensive information about the levels of

various phthalates in the multitude of possible sources, the results of such modeling studies must be scrutinized carefully. For example, if the contributions of some sources, such as breast milk, are based on reliable ingestion data and those of others, such as plastic toys, are based on worst case assumptions, then it is quite likely that the contribution of the latter source will be overestimated and the contribution of the former underestimated. This is of particular concern for exposures of infants and young children, age groups for whom data are often the least available.

Estimating exposures based on biomonitoring data

The other exposure assessment methodology is biomonitoring, which provides direct measures of the amount of each phthalate or phthalate metabolite in human body fluids; e.g., urine, blood, and/or tissues. These fluid or tissue levels must then be translated into exposures. This conversion requires knowledge of the relationship between the magnitude of the phthalate exposure and the amounts of parent compounds and/or metabolites found in the fluids or tissues. In the past seven or eight years, most of the biomonitoring measurements have focused on phthalate metabolites rather than the parent compounds. Because there are significant gaps in knowledge regarding the metabolism and fate of phthalates, it is often not clear which metabolite is the most appropriate analyte. Since the choice of metabolite may have a significant influence on the exposure estimate, literature exposure values may vary significantly when they are based on different metabolites (Calafat and Needham, 2008). An additional source of uncertainty is that the conversion from body fluid concentrations to exposure levels is based on data collected from adults and it is not clear how applicable these data are to other age groups, especially

infants and children.

Biomonitoring data indicate that there is significant variability in urine levels, and thus exposures, over time and among populations (Fromme et al., 2007a). As in modeling studies, the choice of metric is an important one. Using mean urine levels will lead to a lower exposure value than if higher urine levels; e.g, 95th percentile, are used. However, in contrast to the modeling situation, it is possible to quantify the impact of the choice of metric since biomonitoring studies have been performed on large populations and thus good estimates of urinary phthalate level distributions are available. When this has been done, it appears that the 95th percentile values are approximately 4-5 times higher than the mean values (CDC, 2005). This ratio is much smaller than that between the mean and 95th percentile exposure estimates based on modeling. Thus, biomonitoring provides more scientifically defensible values for exposure magnitudes.

Another problem with biomonitoring data has arisen because different researchers have chosen to use different factors to calculate the exposure levels that correspond to the measured urinary phthalate concentrations. Researchers in the U.S. have selected factors that result in significantly lower exposure numbers for some phthalates, generally by a factor of about five for mean values, than those reported by researchers in Germany and Korea (Koch et al., 2003; Koo and Lee, 2005; David, 2000). However, there appears to be a closer correspondence across countries of 95th percentile values than of the means (Fromme et al., 2007 b). In addition to differences in exposure values due to different measurement approaches, it does appear that exposures to some

phthalates are higher in Germany and Korea than in the U.S.

In addition, the time of day at which measurements are made can have a very significant impact on the results because certain activities, such as use of personal care products, are likely to occur mainly at certain times of the day (Duty et al., 2005). While this effect on the data may be small when a large population is studied, it could be significant when biomonitoring is performed on smaller samples. Skewing of the results by making measurements reflecting very recent exposures could lead to an overestimate of average exposures and thus to the conclusion that risks are higher than they actually are.

Another significant limitation of biomonitoring is that it is usually based on a single sample at a particular date and time and so does not provide information about the time course of exposure in that individual or population. This is particularly true for compounds, like phthalates, that are readily metabolized and can change rapidly in concentration over time. In addition, ethnicity and gender, as well as socioeconomic variables, have impacts on exposure (Koo et al., 2002) and these are often not reflected in the data which are generally summary values for particular age groups. Further, biomonitoring data are not generally available for some populations thought to be particularly at risk; i.e., infants and very young children. In addition to the limitations in providing an accurate picture of exposure magnitudes and time course, the fluid or tissue levels do not provide information about sources or routes of exposure. As a result, biomonitoring data cannot be used alone to provide the basis for determining relative source contributions for particular phthalates or for particular populations.

Summary

Each of the methodologies for estimating exposure has its own strengths and limitations. In general, biomonitoring provides more accurate estimates of the magnitudes of exposures since it is based on actual measurements of phthalates in humans. While one analysis which compared the results of applying both biomonitoring and modeling in similar populations concluded that they both provide similar estimates of the magnitude of exposure (Wormuth et al., 2006), these conclusions are based on comparisons of a limited number of studies. A comparison of different modeling approaches has shown that these can produce quite different results (Franco et al., 2007); hence, such a similarity between biomonitoring and modeling exposure values may be fortuitous. Thus while there are serious questions about the use of modeling for determining the magnitude of exposure, this approach is clearly better for estimating sources of exposure and for providing information about the time course of exposure - keeping in mind the caveat about the validity of using modeling estimates for source attribution when estimated exposures by different routes are calculated by different methods. With these considerations in mind, the data that have been used for assessing exposure to the various phthalates of concern will be presented and discussed in the risk characterization section.

Toxicity Assessment

While the phthalate esters share some structural similarities, the data reveal that the types of toxic effects that they produce in experimental animals exposed to high phthalate doses differ from phthalate to phthalate (Lee and Koo, 2007). Some researchers claim that the mechanisms of action and effects of some groups of phthalates are similar enough that they can be considered additive (Gray et al., 2000). Given such claims, the risk characterization section of this paper will include not only an assessment of the toxicity data on each ester individually, but also an evaluation of whether these data provide a sound basis for the claims of additivity that have been made.

Toxicity assessments are generally performed to provide input for risk management decisions

rather than to provide best estimates of risk. As part of this process, studies are performed to determine the lowest daily dose that causes adverse effects in the most sensitive species. These studies are conducted by exposing laboratory animals, usually rats and mice, to high doses of the agent of concern to determine what types of effects might result and at what doses these effects occur. Often, safety and/or uncertainty factors are applied to these lowest observable adverse effect levels (LOAELs) or highest observable no adverse effect levels (NOAELs) to calculate acceptable levels to which humans may be exposed. These values, which may have a variety of names; e.g., Reference Dose or Tolerable Daily Intake, go beyond the science to incorporate margins of safety that reflect the policies of the agencies that utilize these values for risk management. Thus, the acceptable exposure value may vary from country to country or agency to agency (TERA, 2008).

To avoid this issue of variability based on policy, and to keep as close to the science as possible, the approach in this article is to use the experimentally based NOAELs and LOAELs to represent the result of the toxicity assessment for each phthalate. These values have some built-in conservatism because they are based on high dose studies of the most sensitive species, not ambient doses administered to animal surrogates thought to be most similar to humans. Indeed, the studies on those species most similar to humans, primates, suggest lower toxicity values than those based on rodent (or, in one case, canine) data which have been used by the various evaluation panels (Matsumoto et al., 2008). Thus, the toxicity values that have been chosen by these groups implicitly contain margins of safety and so are likely to overstate the potency of the chemical under study.

As pointed out earlier, although high dose studies in animals suggested that phthalates might cause liver cancer in humans, careful consideration of the mechanism of action, peroxisome proliferation, led to the conclusion that the animal studies were not relevant to humans. Consideration of other possible mechanisms of cancer causation also suggests that they are unlikely to cause cancer in humans. For example, phthalates do not appear to be mutagenic and so would not cause cancer through effects on genetic material. As a result of this analysis expert panels have not considered phthalates as significant human cancer risks; instead, the toxicological assessments have focused on other endpoints, especially reproductive and developmental effects.

There are a number of commonalities among expert groups in the U.S. and Europe in the choice of LOAEL and/or NOAEL values to represent the toxicity of each of the phthalates. As will be seen from the citations, for some phthalates, the toxicity values are based on critical studies that are over ten years old. While more recent phthalate assessments may be based on newer toxicity data, the resulting risk evaluations are not significantly different from those of earlier panels. However, when there are differences, the toxicity values used in the risk characterization section will reflect the most recent panel evaluations. As mentioned above, these values are designed to be protective so that the conclusions drawn based on these will not reflect best estimates of risk but most likely upper bounds of risk.

Risk Characterization

The preceding general analysis provides the framework for characterizing the risk for each

phthalate individually and in combination with other phthalates. The risk characterizations will be largely based on the toxicity and exposure assessments that have been performed by a number of expert panels in the U.S. and Europe.

As previously stated, there is a great deal of commonality among expert groups in the critical studies chosen for estimating toxicity values, although there are some disparities. In all of these panel reports, the studies upon which toxicological no and lowest effect values are based are laboratory animal experiments. The toxicity values selected for the risk characterizations in this paper represent the no and lowest effect levels at which effects occur in these critical studies of the most sensitive species or strain.

Exposure estimates show somewhat less commonality among consensus reports than toxicity values since they are largely based on modeling where differences in assumptions can lead to significant variations in exposure values. In large part, this is because comprehensive biomonitoring data were not available to the panels. Because of the importance of biomonitoring results for exposure assessments, they will be included in many of the risk characterizations in this paper (Calafat and McKee, 2006). When biomonitoring is used in the risk characterizations, the U.S. approach to the conversion of urinary levels to exposure values will be adopted.

As mentioned previously, the contention has been made that additivity among phthalates leads to higher risks than calculated from individual phthalate assessments. While, proponents of this view have not provided a quantitative assessment of how this might affect overall risk in

humans, additivity is often mentioned in both scientific and popular publications so it is appropriate to address this issue. In light of this, additivity will not be addressed with regard to individual phthalates but will be addressed in a separate section of the risk characterization.

In addition, while epidemiological investigations are often referenced or discussed in the expert panel reports or review articles, they are controversial and so do not provide convincing evidence that can be used in reaching a consensus with regard to individual phthalates. However, since epidemiological investigations on possible phthalate effects in humans are often cited in popular reports and sometimes cited in expert panel deliberations, they are worthy of consideration and will be discussed in a separate section of the risk characterization.

In the individual phthalate evaluations below it is important to remember that expert panels based their conclusions on exposure and toxicity values reflecting conservative assumptions; e.g., worst case scenarios. This approach leads to evaluations that significantly overstate the risk compared with estimates using the best science. Thus, if a group consensus is that there is little or no risk from a particular phthalate, this provides strong support for the conclusion that this phthalate is unlikely to cause adverse effects in humans.

Di-n-octyl Phthalate (DnOP)

DnOP is found in a variety of products, including building materials, vinyl gloves and hoses, and cements. There are few data on the concentrations of DnOP in these products or in foods, into which it might leach, so it is not possible to use modeling of routes of exposure to calculate

human exposure. Thus, exposure is based on biomonitoring data that have been collected. The most recent sampling of a large sample of the U.S. population above the age of six, based on the DnOP metabolite mono-(3-carboxypropyl) phthalate (MCPP), shows that urinary levels are very low with the 95th percentile level corresponding to an exposure of about one microgram per kilogram per day (ug/kg/day) (CDC, 2005). A biomonitoring study of a limited sample of U.S. children from 12-18 months of age indicates that urinary DnOP levels are below the limit of detection in this population (Brock et al., 2002). Since the lowest detectable value corresponds to an exposure of about 1 ug/kg/day, the actual levels are below this value. No biomonitoring data are available for children younger than twelve months.

There are a limited number of toxicity studies of DnOP although the ones that have been performed indicate that it is of very low toxicity. A NOAEL of 37 mg/kg/day and an LOAEL of 370 mg/kg/day, based on liver effects, has been chosen to represent the chronic toxicity of DnOP (Poon et al., 1997). While questions have been raised about the quality and applicability of available developmental toxicity studies, they do indicate that no such toxicity was produced in mice even at the highest doses administered, 7500 mg/kg/day (Heindel et al., 1989). Similarly, studies on reproductive toxicity in adult rodents indicate that high doses are needed to cause any effects (Kavlock et al., 2002g). In carefully designed studies, no reproductive effects of oral administration of DnOP to mice were observed even at very high doses (NTP, 1985). There are no studies on the carcinogenicity of DnOP.

In summary, the data indicate that DnOP exposure is very low in humans of all ages. Although no biomonitoring data are available from children below the age of one, there are data indicating

that children of this age engage in less mouthing behavior than one to two year olds. Thus, the lack of detection of DnOP in one to two year olds suggests that this would also be the case for younger children. Although the toxicological data are incomplete, they indicate that very high levels of exposure, hundreds or thousands of mg/kg/day, are needed to produce toxic effects. Considering the limits of detection of about 1 ug/kg/day, the ratio of the DnOP doses needed to produce effects in animals to the measured DnOP exposure in humans is extremely high, in the thousands. (See Table 1) Thus, it is clear, even considering the uncertainties and gaps in the data, that the risk from DnOP is not significant. This conclusion supports and extends the original conclusions of the NTP-CERHR panel, based on higher exposures up to 30 ug/kg/day, that there is negligible concern about possible adverse effects of DnOP on humans (Kavlock et al., 2002g).

Di-isodecyl phthalate (DIDP)

DIDP is found in a variety of products, including building materials, vinyl gloves, hoses, artificial leather, wires, cables, toys and cements. Studies of DIDP levels in toys over the past ten or fifteen years indicate that it is not present at all or present in only a small fraction of toys tested (Kavlock, 2002d; ECB, 2003a). Studies assessing DIDP levels in foods, into which DIDP may leach, have not detected this phthalate suggesting that levels in foods are negligible. A recent analysis of phthalates in human breast milk and blood, with a limit of detection of about 1 ug/l, did not detect DIDP in any of the samples. (Hogberg et al., 2008) However, an EFSA panel arrived at an estimate of 7 ug/kg/day based on the limit of detection and worst case assumptions (EFSA, 2005b). Considering that the data reveal that DIDP is infrequently detected in the likely

sources of exposure, this value undoubtedly overestimates the actual exposure. As a result of the lack of adequate human biomarkers until very recently, biomonitoring results on DIDP levels in human urine are not available for any age group. Thus exposure values based on biomonitoring are also unavailable.

Studies of chronic toxicity indicate that some effects on the liver occur at high levels of exposure, above about 75 mg/kg in rats (Hazelton, 1968). The NOAEL in these studies is 15 mg/kg/day. Developmental toxicity studies have been considered by recent expert panels but they have concluded that liver toxicity is the most sensitive effect. Investigations of reproductive toxicity reveal that DIDP does not have adverse reproductive effects on either the male or female reproductive systems (EFSA, 2005b). There are no studies on the carcinogenicity of DIDP.

Considering the absence of data indicating exposure above the limits of detection and the high doses needed to cause any adverse effects in rats, and even higher doses to cause effects in mice, the ratio of the lowest effect level to human exposures is very high, in the thousands. (See Table 1) Thus, there does not seem to be any significant risk to humans from DIDP exposure. This conclusion extends and confirms the consensus of the NTP-CERHR panel and the ECB expert group that there is minimal concern about possible adverse effects of DIDP on humans (Kavlock, 2002d; ECB, 2003a).

Di-isononyl phthalate (DINP)

DINP is a mixture of phthalates with side chains varying in length from 8 to 10 carbon atoms. It is found in a variety of products including building materials, gloves, adhesives, toys and furniture. Studies of levels in toys indicate that it is present at significant, but highly variable concentrations (Babich et al., 2004). Studies of DINP in foods, into which it might leach, have shown that it is present at very low levels and thus foods probably do not represent significant sources of exposure (Wormuth et al., 2006). The most recent investigations of phthalates in human breast milk and infant formula indicate that DINP can be detected in breast milk but not in infant formula (Mortensen et al., 2005). Levels in breast milk were inconsistent from study to study so it is difficult to quantitate the contribution from this source with any confidence (Mortensen et al., 2005). A number of modeling studies have been performed to estimate exposure to infants and children through mouthing of toys. While early estimates based on worst case assumptions suggested that such exposures can be significant - on the order of 100 ug/kg/day - more recent assessments based on more realistic assumptions and better data indicate that DINP exposures from toys are quite low - about 1 ug/kg/day (Juberg et al., 2001; Babich et al., 2004).

The most recent large scale biomonitoring survey in the U.S. of the population above the age of six, indicates that urinary levels are quite low (CDC, 2005). These urinary concentrations correspond to very low exposures - less than 1 ug/kg/day - even for the 95th percentile. A study of U.S. children - 12 to 18 months of age - showed that DINP metabolites in urine were below the limit of detection suggesting that exposure of children at these ages is very low (Brock et al., 2002). These data are consistent with the more recent modeling results mentioned above

showing that plastic objects mouthed by children do not lead to significant exposures. The results of studies of DINP in breast milk, although exhibiting significant variability, suggest that that breast fed infants may experience exposures on the order of 1 ug/kg/day (EFSA. 2005a).

Data from studies of the chronic toxicity of DINP in rats indicate that the liver is the most sensitive organ and the lowest no effect level is approximately 90 mg/kg/day and the lowest effect level is about 360 mg/kg/day (Aristech, 1994). Developmental toxicity studies suggest that somewhat higher doses are required to produce developmental effects in rats (EFSA, 2005a). No effects on reproduction were observed in studies where very high doses were administered to rats (EFSA, 2005a). DINP is carcinogenic in rodents exposed to very high doses over a lifetime. However, data on differences in mechanism of actions between rodents and humans indicate that these results cannot be applied to humans and that DINP is not expected to be carcinogenic in humans (Kaufmann et al., 2002).

Considering that exposures, even in infants and children, appear to be quite low and thousands of times lower than levels causing adverse effects in rodents, it can be concluded that risks from DINP are very low for all populations. (See Table 1) The data indicate that there is unlikely to be any special risk from mouthing of toys since any developmental effects would require DINP exposures that are extremely high compared to that expected from toys. These conclusions confirm and extend the judgments of the Koop panel, NTP-CERHR, CSTEE, and ECB that there is little or no concern about possible adverse effects of DINP on humans (Koop et al., 1999; Kavlock et al., 2002e; CSTEE, 2001a; ECB, 2003b).

Butylbenzyl phthalate (BBP)

BBP is found in a variety of products, including building materials, vinyl gloves, artificial leather and adhesives. However, it is not commonly used in plastic toys so exposures in infants and children from this route are very low (ECB, 2007). Studies of BBP levels in various commodities have shown that foods are the main source of BBP exposure in most age groups, although it has been suggested that ingestion of dusts is a significant source of exposure for very young children (Wormuth et al., 2006). The sources of these dusts are most likely building materials (Bornehag et al., 2005). The most recent investigations of phthalate concentrations in human breast milk and infant formula indicate that BBP levels in these media are non-detectable or extremely low (Mortensen et al., 2005; Zhu et al., 2006). Modeling has indicated that BBP exposures in all age groups are below 1 ug/kg/day (Wormuth et al., 2006).

The most recent large scale U.S. biomonitoring data indicates that BBP levels in the population above the age of six are quite low, corresponding to very low mean exposures - less than 1 ug/kg/day (CDC, 2005). The results of a study of U.S. children - 12 to 18 months of age - indicate that BBP exposures in this age group are also very low although likely higher than exposures in adults. It is estimated that they are on the order of 1 ug/kg/day (Brock et al., 2002).

Data from studies of the chronic toxicity of BBP indicate that developmental toxicity is the most sensitive effect and the lowest dose that will cause this effect is approximately 250 mg/kg/day; the no effect level in this study is 50 mg/kg/day (Tyl et al., 2004). The lowest effect level for reproductive effects is higher.. Studies of the carcinogenicity of BBP in rodents exposed to very

high doses over a lifetime have yielded equivocal results in rats and evidence of non-carcinogenicity in mice (ECB, 2007). Careful evaluation of these results has led scientists to the conclusion that there is no concern that BBP causes cancer in humans (ECB, 2007).

Considering that exposures, even in infants and children, are quite low - thousands of times lower than levels causing adverse effects in rodents - it can be concluded that risks from BBP are very low for all populations. (See Table 1) Since BBP is not routinely found in toys, the mouthing route of exposure is unlikely to make any significant contribution to exposure in infants and young children. These conclusions extend and confirm those of the NTP-CERHR, which stated there was minimal concern and the EU Risk Assessment which stated that there was no concern (Kavlock, 2000a; ECB, 2007). Both of these conclusions were based on higher exposure estimates than appear warranted from more recent biomonitoring data.

Dibutyl phthalate (DBP)

In contrast to the phthalates previously discussed, DBP has not been used as a plasticizer in PVC for a number of years. However, it is used in latex adhesives, as a solvent in dyes, as a plasticizer in cellulose plastics, in coatings of medications and for a variety of purposes in cosmetics. It may also be found in food due to leaching from DBP-containing products that come into contact with food during processing or storage. Use of DBP in plastic toys appears rare because the results of careful analyses of toys indicate that it is either not present or present at very low levels (Kavlock et al., 2002b). From monitoring data, food seems to be the main source of human exposure to DBP although air and dust appear to be significant contributors in infants

and children and personal care products may be significant sources of exposure in teens, especially females (Wormuth et al., 2006). Modeling of source contributions and behaviors suggests that exposures are quite low - between 1 and 5 ug/kg/day (Wormuth et al., 2006).

The most recent large scale U.S. biomonitoring data indicates that DBP levels in the population above the age of six are quite low, corresponding to very low mean exposures - less than 1 ug/kg/day (CDC, 2005). A study of U.S. children - 12 to 18 months of age - also suggests very low exposures to DBP in this age group. While urinary levels indicate that exposures may be higher in this age group than those in adults, they are still quite low - perhaps twice as high as those found in adults (Brock et al., 2002). Studies of phthalates in breast milk, cow's milk and infant formulas indicate that daily exposures from these sources are less than 1 ug/kg/day (Mortensen et al., 2005; Zhu et al., 2006).

Results of studies on the chronic toxicity of DBP suggest that developmental toxicity is the most sensitive endpoint and that the lowest dose that causes this effect in rats is about 250 mg/kg/day with a no effect level of about 50 mg/kg/day (Wine et al., 1997). It requires higher doses to produce effects on reproductive toxicity in rodents (ECB, 2003c; Gray et al., 2006). There are no adequate studies of the carcinogenicity of DBP.

Considering that exposures of all age groups, including infants and children, are thousands of times lower than the lowest effect levels in rats, it seems unlikely that DBP will cause adverse effects in any human age group, including children. (See Table 1) Since DBP is not routinely found in toys or other plastic objects that infants and children may come into contact with, the

contribution of the mouthing route of exposure to any risk is clearly quite small. While the NTP-CERHR panel expressed some concern about DBP, a more recent risk assessment by the European Union concluded that there was no concern, even for breast-fed babies – consistent with the above analysis (Kavlock, 2002b, ECB, 2003c).

Diethylhexyl phthalate (DEHP)

DEHP is found in a variety of products, including building materials, medical devices (such as tubing and drainage bags), and paints and adhesives. It is also found in a variety of food products due to leaching that may occur during food production and storage. DEHP has been used in some toys but not those designed for infants and toddlers. Analytical studies of toys reveal that if DEHP is present it is at very low levels (Kavlock, 2002c). Modeling suggests that food is by far the major non-medical source of exposure in children and adults and that both food and ingestion of dusts are major sources of exposure in infants and toddlers (Wormuth et al., 2006). Studies indicate that daily exposures of infants and children to DEHP from ingestion of breast milk, cow's milk and infant formula are quite low - in the range of 1- 10 ug/kg/day (Mortensen et al., 2005; Zhu, et al., 2006). Modeling assessments suggest that DEHP exposure levels in almost all age groups are below 10 ug/kg/day, although this value may be slightly exceeded in infants (Wormuth et al., 2006).

The most recent large scale U.S. biomonitoring data indicates that DEHP levels in the population above the age of six are quite low, corresponding to very low mean exposures - about 1 ug/kg/day (CDC, 2005). A study of children in the U.S. - 12 to 18 months of age - indicates that

they also experience very low exposures - less than 1 ug/kg/day. While urinary levels suggest that exposures may be as much as twice as high in this age group as in adults, they are still quite low (Brock et al., 2002).

While these data reflect general population exposures, adults and neonates who have undergone a variety of serious medical procedures such as transfusions, dialysis and extracorporeal membrane oxygenation, have experienced much higher exposures to DEHP, although over a limited time period. These exposures may be tens to hundreds of times higher than those experienced by the general population (SCENIHR, 2008).

Results of laboratory studies on the toxicity of DEHP suggest that high doses, of at least 14 mg/kg/day in rats, are needed to cause reproductive and/or developmental toxicity which is the most sensitive effect in rats (Wolfe and Layton, 2003). The no effect level in these studies is 4.8 mg/kg/day. While DEHP causes liver tumors in rodents exposed to high doses over a lifetime, consideration of the mechanism by which this occurs leads to the conclusion that DEHP is not likely to be carcinogenic in humans (IARC, 2000).

Considering that exposures of all age groups are hundreds to thousands times lower than the lowest effect levels in rats, it seems unlikely that DEHP will cause adverse effects in any human age group, including children. (See Table 1) Although the estimated exposure levels from leaching of phthalates from medical devices is high compared to general population exposures, these exposures are short term and are difficult to compare with exposures experienced by

rodents in

laboratory studies. These conclusions are consistent with those of the Koop panel (Koop et al., 1999). The updated NTP-CERHR panel report of 2005 included a decrease in the level of concern for some effects but not others. These new conclusions were based on higher exposure estimates, up to 30 ug/kg/day, than are consistent with biomonitoring data and so are likely to overstate the levels of concern (NTP, 2005; CDC, 2005).

Combined Exposures to Multiple Phthalates

It has been argued that it is not appropriate to assess the risks from phthalates by evaluating each phthalate individually because people are exposed to many phthalates at the same time or during the same day. Further, it is claimed that this approach significantly understates the risk and that a more accurate estimate of risk would result if the exposures were added together and compared with the doses that cause adverse effects in laboratory animals (Gray et al., 2000; Wittassek and Angerer, 2008). The implication is that toxic effects not seen with individual phthalates will be seen in the people exposed to multiple phthalates. Although such a contention may seem plausible, it does not stand up under careful scrutiny.

First, phthalate exposures are generally many hundreds or many thousands lower than the doses required to produce adverse effects so that adding the exposures to a number of phthalates together will not lead to a total exposure that approaches the effect level for even the most potent phthalate. Second, it is not clear that exposures from different sources are additive in humans. For example, a study of phthalates in personal care products showed that the levels of some

phthalates were reduced in individuals who used phthalate containing lotions compared with those who did not (Duty et al., 2005). Third, and perhaps most important, not all phthalates affect the body the same way so that it is not scientifically appropriate to combine their exposures (Lee and Koo, 2007). Indeed, a European Food Safety Authority expert panel concluded that additivity was not appropriate on these grounds (EFSA, 2005c).

Although there is a more recent study that suggests additive effects of two phthalates at very high doses in animals (Howdeshell et al., 2007), it is not clear that this is applicable to low doses in animals, much less humans, or to other phthalates. Thus, the contention that combined exposures to low levels of multiple phthalates in humans will lead to toxic effects not expected from individual phthalate exposures is not scientifically persuasive.

Evidence from Epidemiological Studies

A number of studies have examined possible impacts of phthalates on human reproduction, mainly the male reproductive system. While this research reveals that phthalates may be associated with changes in some parameters associated with male reproduction; e.g., sperm concentration, the data are not consistent across studies and also sometimes in conflict with results gathered in experimental animals (Matsumoto et al., 2008). Because of these limitations, the data are difficult to interpret and do not support a link between phthalates and changes in human reproductive parameters.

In addition, these high dose studies provide evidence of changes in parameters rather than

adverse effects on reproductive performance. Thus, they do not provide the type of evidence needed to assess what, if any, effects phthalates have on male reproduction in humans at ambient levels of exposure. There are very few studies on possible effects of phthalates on human female reproduction but those that have been performed do not provide convincing evidence of any adverse effect (Matsumoto et al., 2008). This is consistent with animal studies suggesting that very high doses are required to have any impact on female reproductive parameters.

Two epidemiological studies on the potential for phthalates to adversely affect the reproductive system of children have been widely cited. One looked at the relationship of phthalate levels and the anogenital index (AGI) (Swan et al., 2005) and the other on phthalates and cryptorchidism and hormone levels (Main et al., 2006). The former study falls far short of showing adverse impacts from phthalates for a number of reasons including that the normal variability of the AGI in humans has not been established, and that the data do not provide evidence of an impact on reproductive performance (McEwen and Renner, 2006; Kamrin, 2007). The latter study did not find any association between phthalate levels and cryptorchism but did find some correlations between some phthalates and some hormone levels. It is not clear whether these have any functional significance.

Some limited epidemiological data from studies of adults and neonates who have been exposed to relatively high doses of DEHP from medical procedures indicate that they do not exhibit the adverse effects seen in animals (Rais-Bahrami et al., 2004; Hack et al., 2002). Thus, they do not support the claim that low ambient levels of DEHP can cause adverse effects in humans.

Summary

Based on the analysis presented in this section, the lowest levels at which toxic effects occur in the most sensitive animals are very much higher than the doses to which humans are exposed (calculated from either measurements of phthalate concentration levels in sources or from phthalate levels in human fluids). The ratio between the lowest effect level and exposure is not the same for each phthalate since they are not equally potent based on laboratory animal studies and also because exposures vary among phthalates. Indeed, the lowest adverse effect levels vary by at least a factor of ten from phthalate to phthalate. DEHP appears to be the most potent phthalate based on the animal data and DEHP exposure levels appear to be at least as high as those of the other phthalates so this agent provides the best test for the contention that phthalates cause adverse effects in humans at ambient levels.

DEHP was the subject of a 2008 expert panel report issued by the European Commission Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR, 2008). Although the focus of the report was on DEHP in medical devices, the conclusions reached have broader implications. The lowest adverse effect level and the best estimates of DEHP exposure levels agreed upon by the panel are consistent with those cited previously in the section on the risk characterization of DEHP. In addition to re-examining the literature on experimental animals, the group looked very carefully at epidemiological studies designed to examine possible male and/or female reproductive effects from DEHP. The panel concluded that the data regarding a wide range of reproductive effects are either inconclusive or contradictory (or both) and so such effects have not been established in humans.

This panel report, based on an extensive review of research on the most potent phthalate, DEHP, provides strong support for the conclusions reached above about DEHP; that is, there is little or no cause for concern for adverse effects from exposure of the general population to DEHP. Further, there is no firm evidence that any effects have occurred or are likely to occur in the adults and infants most heavily exposed to DEHP as a result of intensive medical procedures. If this phthalate does not pose a significant risk, this strongly suggests that the less potent phthalates are even less likely to be of concern to humans.

Public Health Implications

As was discussed in the risk characterizations of the individual phthalates, the lowest dose that causes effects in animals is in most cases thousands of times higher than the exposures that humans, including infants and children, experience. For DEHP, this dose was about a thousand times higher than non-medical human exposure levels. In addition, there is no convincing evidence that links adverse effects in humans to phthalate exposures, even for those who were exposed to very high levels during medical procedures.

In light of these conclusions, the current and proposed regulations effectively banning phthalates in toys and other plastic objects that infants and children may come into contact with are unlikely to provide any reduction in the risk, if any exists, from phthalate exposure. Thus, these

regulations are not likely to provide any public health benefit. In addition, based on current data and understanding, any broader regulations aimed at other sources of phthalates are also unlikely to be of benefit to the health of the public.

In addition to the lack of public health benefit from the proposed and enacted regulations, there is the strong possibility that these regulations will result in negative impacts on public health. The replacement of phthalates with other compounds for which much less toxicity data is available and which have not been subject to the same degree of scrutiny as phthalates leaves open the possibility of yet unknown risks. Also, the combination of properties that make phthalates useful in commercial products; e.g., providing flexibility of plastics as well as transparency, are likely to be difficult to duplicate and thus substitute products may be inferior in quality . This is of particular concern with regard to medical devices and is reflected in the reluctance of medical professionals to use substitutes for phthalate plasticized materials in some applications. In sum, the benefits of phthalates for public health and the lack of comprehensive toxicological information on substitute compounds leave open the possibility that replacement of phthalates may lead to a net reduction in the overall health of the public.

The outcomes of the expert panel deliberations provide little, if any, scientific justification for the regulation of phthalates in toys and other plastic objects to which children may be exposed. This raises the question of what rationale has been used in the justifying the controls that have been enacted. An examination of the California approach to chemical regulation provides some insight into this. California's Proposition 65, which was enacted over twenty years ago, is a

paradigmatic example of this approach. Under this Proposition, the state required the development and issuance of lists of chemicals causing cancer and/or reproductive/developmental effects in any species and the posting of warnings to inform people who may be exposed to any of the listed chemicals at any level. Since dose is unimportant, it is clearly hazard and not risk that is the basis for the approach; i.e., the regulatory criterion is the type of effect rather than the likelihood that this effect will occur. A similar approach appears to guide the phthalates regulations since they are based on the presence of phthalates rather than the potential for adverse effects from phthalates in particular products.

Discussion

In the years since the 1999 Koop report on DEHP and DINP and the NTP-CERHR evaluations of seven phthalate esters conducted from 1998-2000, there have been a large number of new studies on possible toxic effects of phthalates. Many of these have been incorporated into the deliberations of expert panels, including those representing a variety of European Commission scientific agencies. The latest of these, focused on DEHP, appeared in early 2008. Although

there have been some minor changes and refinements in the evaluations over time, all of the additional research and deliberations have not significantly altered the earlier assessments of phthalate risks.

The summaries presented in the risk characterization section thus reflect the accumulated judgments of a large number of scientists who have studied the data carefully over more than a decade. As the citations show, while many of these judgments are based largely on research that was performed in the years previous to 2000, they also reflect additional studies that were conducted more recently in response to requests from expert panels for the scientific community to fill gaps in the data - including epidemiological investigations. Overall, although the laboratory data suggest that the phthalates vary in potency, the risk from even the most potent of them, individually or in combination, is quite small for all age ranges in the general population. Although exposure levels are much higher for the very small sub-population of individuals, both adults and neonates, undergoing certain medical procedures, there is little evidence of adverse effects in this population as well.

Despite these conclusions resulting from a large effort in the U.S. and Europe to investigate and evaluate possible adverse effects of phthalates, there have been increasing efforts to regulate these compounds. In the EU, this resulted in regulations essentially banning six phthalates in plastics to which infants and children may be exposed. These took full effect in 2005 and in the past few years a number of states in the U.S. have attempted, in some cases successfully, to emulate this regulation. It appears that this trend will continue although the scientific evidence

very strongly suggests that such risk management efforts are unlikely to lead to any improvement in public health.

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Table 1. Comparison of Phthalate Exposure and Toxicity Values

Phthalate ester	LOAEL (mg/kg/day)	NOAEL (mg/kg/day)	Estimated mean exposure (mg/kg/day)	Ratio of LOAEL to exposure	Ratio of NOAEL to exposure
DnOP	370	37	0.001	370,000	37,000
DIDP	75	15	0.001-0.007	10,714-75,000	2,140-15,000
DINP	358	88	0.001	358,000	88,000
BBP	250	50	0.001	250,000	50,000
DBP	256	52	0.001-0.005	256,000-51,200	10,400-52,000
DEHP – general population	14	4.8	0.001-0.010	1,400-14,000	480-4,800
DEHP – medically exposed	14	4.8	0.100-2.0	7.0-140	2.4-48

Note: See text for sources for exposure and toxicity values