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[Manuscript Cover Page]

Dempster-Shafer Theory Applied to Regulatory Decision-Making for Safer Alternatives to Toxic Chemicals in Consumer Products

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[Abstract]

Regulatory agencies often face a dilemma when regulating chemicals in consumer products – namely, that of making decisions in the face of multiple, and sometimes conflicting, lines of evidence. We present an integrative approach for dealing with uncertainty and multiple pieces of evidence in toxics regulation. The integrative risk analytic framework is grounded in Dempster-Shafer (D-S) theory that allows the analyst to combine multiple pieces of evidence and judgments from independent sources of information. We apply the integrative approach to the comparative risk assessment of Bisphenol-A (BPA) based polycarbonate and the functionally equivalent alternative, Eastman Tritan^{TM} copolyester (ETC). Our results show that according to cumulative empirical evidence, the estimated probability of toxicity of BPA is 0.034, whereas the toxicity probability for ETC is 0.097. However, when we combine extant evidence with strength of confidence in the source (or expert judgment), we are guided by a richer interval measure, [Bel(t), Pl(t)]. With the D-S derived measure, we arrive at various intervals for BPA, with the low-range estimate at [0.034,0.250], and [0.097,0.688] for ETC. These new measures allow a reasonable basis for comparison and a justifiable procedure for decision-making that takes advantage of multiple sources of evidence. Through the application of D-S theory to toxicity risk assessment, we show how a multiplicity of scientific evidence can be converted into a unified risk estimate and how this information can be effectively used for comparative assessments to select potentially less toxic alternative chemicals.

KEY WORDS
Bisphenol-A, Consumer products, Dempster-Shafer theory, Green chemistry, Regulatory Policy, Risk assessment, Risk perception, Safer alternatives, Scientific uncertainty, Toxic chemicals

[Main Text]

1. INTRODUCTION

Consider a chemical 'A' that has long been used in the manufacture of one or more popular consumer products. The toxic effects of 'A' on human health and environment have become a growing concern. Influenced by some scientific evidence and vocal advocacy groups, the public clamors for a regulatory response, whereas manufacturers of 'A' vouch strongly for the safety of their product. Another manufacturer recently introduced a functional alternative chemical 'B', hoping to win over consumers who are now sensitized and anxious over 'A'. However, there is little or no empirical evidence to support the assumption that chemical 'B' is non-toxic over the entire course of its material life cycle.

How should decision makers responsible for protecting public health and environmental quality proceed under this increasingly common scenario? The urgency of the question escalates as regional bodies such as the European Commission (EC) and states such as California struggle with comprehensive chemical regulatory initiatives including the EC's Registration, Evaluation, Authorization and Restriction of Chemical substances (REACH) and California's Green Chemistry Law.

In the scenario posited above, the toxicity of 'A' still remains ambiguous despite a large amount of non-conclusive published research. On the other hand, little toxicological evidence is available for the chemical substitute 'B'. The paucity of research studies on alternative chemicals lowers confidence in anchoring regulatory decisions on unreplicated evidence. However, decisions must be made in a timely manner to protect vulnerable populations from adverse health effects.

The debate on the nature of scientific evidence on toxicity risk and regulatory response to the presence of Bisphenol-A (BPA) in consumer products mirrors the scenario presented above (Myers et al. 2009). BPA has long been an ingredient of numerous consumer products characterized as hard and clear plastics used as containers for both infant and adult foods and drinks. At issue are conflicting results of many risk assessment studies and the apparently selective interpretation and translation of those studies into regulatory policies at different jurisdictions across state and national boundaries.

Through this research, we develop a comparative risk assessment model that can guide regulatory decisions on controversial chemicals such as BPA and proposed chemical substitutes like Eastman Tritan^{TM} copolyester (ETC). We base this model on Dempster-Shafer theory (D-S theory), which allows the combination of multiple pieces of evidence from independent sources of information. The new comparative risk assessment model can be used as an analytical tool for selecting less toxic alternatives for consumer products by regulatory agencies.

2. BRIDGING THE GAP BETWEEN SCIENCE AND POLICY ON TOXIC CHEMICALS

The time-lag between initial evidence of adverse impacts of chemicals widely used in society and regulatory response to prevent damage through human and environmental exposures has traditionally been very long, resulting in accumulation of diseases in the population and environmental pollution, as exemplified by the cases of DDT (Dichlorodiphenyltrichloroethane) lead (Pb), CFCs (cholorofluorocarbon compounds), and carbon dioxide (Carson 1962; Ogunseitan 1999; Ogunseitan 2007). The lengthy response time is due in part to the

environmental regulatory strategy of 'innocent until proven guilty' in contrast to the 'precautionary principle' that is more aligned with the preventive focus of public health. In most cases, the protraction of regulatory response time is driven by uncertainty in scientific evidence, controversy on the interpretation of evidence, and variegation of public risk perception (NAS 2009).

The trajectory of regulatory decision-making regarding BPA is not an exception. Since vom Saal and colleagues reported the possible adverse health effects of exposure to BPA at low doses in 1997, the world leading entities' regulatory actions against BPA use have emerged only in recent years (vom Saal et al 1997). In October 2010, the government of Canada became the first jurisdiction in the world to declare that BPA is toxic, and since April 2008, the chemical was no longer tolerated in plastic feeding bottles used by infants and children. The EC announced a ban on the use of BPA in infant products in 2010. China and Malaysia joined Canada and the EC's regulatory decision to ban BPA in July, 2011. Meanwhile, it was not until July 2012 that the United States Food and Drug Administration (FDA) decided to ban BPA use in baby bottles and children's drinking cups. Despite the fact that National Toxicology Program (NTP), a branch of the National Institute of Environmental Health Science (NIEHS), concluded in 2008 that it has "some concern for effects on the brain, behavior, and prostate gland in fetuses, infants, and children at current human exposures to bisphenol A", the U.S. federal agencies, including the United States Food and Drug Administration (FDA) and the National Institutes of Health (NIH) delayed conclusions about the risks associated with BPA until the results of further studies funded in excess of $50 million (NTP 2008) .

Many factors contribute to delays in regulatory responses to chemical risk factors, and to regulatory disparities across regional and international boundaries, but disagreements over the

quantity, quality, and source of scientific data is the most cogent (NAS 2009). Authoritative toxicology research programs such as the US NTP and the Europe's REACH program that perform chemical risk assessments sometimes differ in their conclusions but they also occasionally change their opinions regarding toxicity risks.

This ad hoc dimension of regulatory decision-making over potentially harmful chemical substances impairs the ability of policy makers to articulate comprehensive and integrative risk management decisions. This inability can significantly appear among policy-makers in nations that lack the infrastructure and trained personnel to implement rules and regulations of toxic chemicals because they may prefer to wait final regulatory decisions of the world's leading entities such as the EC before taking any action.

Scientific study results also put policy makers in similar situations. Disparities in the presentation of toxic risks in scientific studies require a certain level of inquiry to make regulatory decisions over chemical substances. Toxicity information is typically not presented as a binary variable (toxic or non-toxic) because of the powerful influences of contextual biological and social factors such as dose, exposure route and frequency, and effect modifiers including genetics, diet, and behavior. These contextual issues can underpin difference in perception and acceptability of toxicity risks, as demonstrable with the recent introduction of DDT to combat malaria despite prior global ban on the chemical (Curtis 1999; Roberts et al 2000; WHO 2011).

The complexity of risk assessment processes is compounded by the lack of consensus on the definitions of risk; boundaries of multi-level routes of exposure; identity of vulnerable populations, organisms, and environmental systems; and the variable interactions among multiple risk factors and risk modifiers (Dourson et al. 2002; Illing 2001). In response to extensive toxicological research and the inherent complexity of risk characterization, regulatory

agencies typically rely on expert opinions to guide decisions on restricting or banning particular chemicals from commerce. The general assumption that expert opinions are independent of social movements, advocacy, public opinion, and institutional interests has been questioned in the literature (Hoberg Jr. 1990; Kasperson et al. 1988; Slovic 1999).

Comparative assessment of safer alternatives to chemicals known to pose toxicity hazards in consumer products forms the cornerstone of recent initiatives such as the California's Green Chemistry Initiative to regulate chemicals. The substitution of a known toxicant with a relatively understudied alternative chemical has led to numerous costly mistakes including the use of MTBE (methyl tertiary-butyl ether) as an alternative additive to gasoline, after the phase-out of tetraethyl lead (McGarity 2004; Von Krauss and Haremoës 2002). In efforts to guide the transition to safer alternatives for a known toxic chemical in commerce, several methods for alternatives assessment of chemicals are being proposed by researchers (e.g., at the Lowell Center for Sustainable Production Framework for Alternative assessments); or regulatory agencies (e.g., U.S. EPA's Design for Environment's Cleaner Technology Substitutes Assessments; and the State of California Department of Toxic Substances Control, regarding the landmark California Safer Consumer Products Act, popularly known as the Green Chemistry Initiative). . However what these proposed approaches often overlook is the fact that final conclusions on the toxicity of controversial chemicals often remain unsettled or information on proposed alternative chemicals is typically not as detailed as for the primary chemical being phased out. Zeeman et al. (1995) reported, for example that ecotoxicity data are available only for approximately 5% of the chemicals submitted to the U.S. EPA annually.

In chemical toxicity risk assessment practice, controversies and uncertainties generally tend to be assumed to be absent. Controversies are compromised by choosing a piece of evidence

or by using weighted or unweighted averages and uncertainties are treated and eliminated using techniques such as default assumption, uncertainty propagation, sophisticated Quantitative Uncertainty Analysis (QUA) and expert elicitation. These approaches have been mainly applied to exposure assessments. As the definition and scope of risk is being diversified or broadened, new sources of uncertainty have continued to emerge and many identified uncertainties remain to be characterized. Ways to effectively tackle uncertainties are reported insufficient in spite of more than three decades of efforts (NAS 2009).

Our research is concerned with how to accommodate controversies and uncertainties in scientific or policy judgments on a chemical's toxicity from multi-level institutions for a third-party (eg. policy makers in developing countries)'s prompt regulatory action decision. We focus on how controversies over a chemical of interest and the paucity of information available on alternative substances can be codified in the estimation and comparison of the potential for toxicity and the perception of the risks associated consumer products. We explore a new model for integrating of scientific and policy uncertainties and disagreements in toxicity risk assessments. We posit that D-S theory allows us to take into account variability and uncertainty in scientific opinions and disparities in regulatory decisions regarding chemical toxicity.

3. DEMPSTER-SHAFER THEORY

Dempster (1967) and Shafer (1976; 2002) concurrently developed D-S theory to integrate the concept of the degrees of belief and discrete evidence into Bayesian probability theory, thereby offering a mathematical solution to the problem of combining multiple sources of evidence. D-S theory has been exercised in a wide range of areas such as artificial intelligence

and expert systems for decision-making (Beynon et al. 2001), engineering applications for safety and risk assessment (Gao et al. 2011; Sun et al. 2006) and accounting management and information systems (Shenoy and Shenoy 2002). But to our knowledge, the potential of D-S theory, as an emerging and powerful method to take on weight of evidence and uncertainty more directly, has not previously been used for chemical toxicity risk assessment. In the following section, we discuss the three basic components of D-S theory, namely basic probability assignment, Dempster's rule of combination, and the belief and plausibility function.

3.1 Formal definitions and Nomenclature

Given an evidence space (analogous to a probability space), $(X, 2^X, m)$, X is defined as the universal set of all possible states of the system under consideration. The power set, 2^X, indicates the set of all subsets (also called focal elements) of X, including the empty set, Ø.

The function, $m: 2^X \rightarrow [0,1]$, demonstrates a mapping from the power set to the line segment bounded by 0 and 1, where

$$m(\emptyset) = 0$$

$$\text{and} \quad \sum_{A \in 2X} m(A) = 1 \qquad [1]$$

The above expression for the basic probability assignment or *bpa*, *m*, is most clearly interpreted as the proportion or total fraction of evidence supporting the proposition that the true state of affairs is included in *A,* but not in any particular subset of *A*.

As an example, we can consider the hypothetical case of 100 eyewitness accounts of a bank theft. If there were 25 eyewitnesses, each of whom testify that the bank robber wore a blue, yellow, green, or either-green-or-blue shirt respectively (the last category stemming from the fact that 25 of the eyewitnesses are color blind vis-à-vis the colors green and blue). Then, for example, m(blue) = 0.25, m(blue or yellow) = 0, m(green or blue) = 0.25.

In our use of belief theory, we allow the use of a weighting factor or index of credibility, ranging from 0 to 1, assigned to each source of evidence (or 'eyewitness' or 'expert' in the above example). This weighting factor can be interpreted in the light of the above evidence-based framework, too − e.g., the proportion of times the source or expert predicted something that was proven true or valid in the past. Thus, we introduce the notion of 'credibility' of source of evidence into the formal theory. For instance, suppose that an expert testifies that chemical 'Y' is toxic. According to a traditional probability approach, the chance that chemical 'Y' is toxic might then be equated to one, $p(A)$=1. On the other hand, D-S theory assigns different probabilities to the same statement depending on our degree of confidence in the evidence (i.e., here the degree of belief in the expert). If our degree of belief in the expert is 0.8 (on a scale of 0 to 1, with 1 representing absolute trust in the source), the mass value of the statement that chemical 'Y' is toxic is 0.8 and denoted as $m(A) = 1 \times 0.8 = 0.8$. This value can be interpreted

simply as the likelihood that chemical 'Y' is toxic when considering the credibility of the expert. It is important to be aware that the remaining mass value of 0.2 does not indicate the chance of 'Y' being a non-toxic substance but rather the degree to which its true state is 'unknown'.

[Table 1. here]

Table 1 demonstrates the difference between traditional probabilities and basic probability assignments. If the degree of belief in an expert is equal to 1, $m(A)$ becomes equal to the probabilities obtained from Bayesian theory.

The theory then posits two measures, represented by *Bel* (or belief) and *Pl* (or plausibility) that provide lower and upper bounds, respectively, of the strength of evidential support for the proposition, A. Formally, the definitions are as follows:

$$Bel(A) = \sum_{B \mid B \subseteq A} m(B) \qquad [2]$$

and

$$Pl(A) = \sum_{B \mid B \cap A \neq \varnothing} m(B) \qquad [3]$$

Hence, *Bel* represents the amount or proportion of all evidence that would directly support the proposition, A, and *Pl* represents the evidence that does not contradict or might conceivably be consistent with proposition A. And from equation [3], it follows that

$$Pl(A) = 1 - Bel(\bar{A}),$$

where $\bar{A}$ represents the contrary hypothesis, i.e., that A is not true.

3.2 Dempster's Rule of Combination

The combined probability from two or more pieces of evidence can be calculated by Dempster's combination rule {equation [4]}. The sum of the combined *bpa*s, where the intersection of evidence supports the statement of interest, is divided by (1 – K) as a normalization factor. This combined basic probability mass is called 'joint mass' and has been denoted as $m_{1,2}$(A) in [4]. K represents basic probability mass associated with conflicting evidence. This is determined by summing the products of the *bpa*s of all sets where the intersection is null (empty sets).

$$\mathrm{m}_{1,2}(\emptyset) = 0$$

$$\mathrm{m}_{1,2}(A) = (\mathrm{m}_1 \oplus \mathrm{m}_2)(A) = \frac{1}{1-K} \sum_{B \cap C = A \neq \emptyset} \mathrm{m}_1(B)\mathrm{m}_2(C) \quad [4]$$

Where

$$K = \sum_{B \cap C = \emptyset} \mathrm{m}_1(B)\mathrm{m}_2(C)$$

Another way to state the above combination is to understand it as the combination of two evidence spaces, (X_1, 2^{X1}, m_1) and (X_2, 2^{X2}, m_2), to produce a combined evidence space (X_{12}, Y, m_{12}), where $X_1 = X_2 = X_{12}$ and Y = {S| S = B∩C where B=X_1 and C∈X_2}. We will proceed with the use of the above rule of combination, while acknowledging possibilities of other rules.

Table 2 shows an example of calculation using Dempster's rule of combination. The statement of interest can be "substance 'Y' is toxic (a set A)". $m_1(B)$ and $m_2(C)$ are the basic probability assignments for all the subsets from each piece of evidence (evidence B and evidence C). To calculate the combined basic probability assignment for a particular cell, simply multiply the masses from the associated column and row. The shadowed cells in Table 2 are the subsets that satisfy the condition that the intersection between evidence B and evidence C supports the statement that substance 'Y' is toxic (B∩C=A). The sum of those sets is 0.92. The gridded cells represent the empty sets (B∩C=Ø). The sum of the empty sets is equal to zero, meaning *K* equals to zero. The joint mass value is 0.92 (0.92/(1−0) = 0.92), which is the *bpa* that substance Y is toxic taking into account two pieces of evidence. In the example above, $Bel(\bar{A})$ is equal to zero since there is no body of evidence asserting that 'Y' is non-toxic. Therefore *Pl* (*A*) is equal to one and the interval can be demonstrated as [0.92, 1.0]. It can be interpreted that the likelihood that substance 'Y' is toxic is located between 0.92 and 1.0.

4. BACKGROUND INFORMATION ON BISPHENOL-A AND ALTERNATIVE COPOLYESTER

Bisphenol-A (BPA) is a key ingredient of polycarbonate (PC) plastic and epoxy resins used to fabricate ubiquitous consumer products includeing water and food containers. Annual production of BPA exceeds 3 billion kilograms (Susiarjo et al. 2007).

Plastic products tend to leak BPA, contributing to ingestion and distribution of the chemical in the body (Brotons et al 1995; Feldman and Krishnan 1995). Carefully controlled studies have demonstrated that most people have measurable levels of BPA in the parts per billion range. Lakind and Naiman (2010) estimated that the median daily intake for the U.S.

population is approximately 34 ng/kg-day, and the Centers for Disease Control and Prevention (2009) reported that low levels of BPA were detected in 92.6% of the urine samples in a survey of the general U.S. population. In addition, BPA has been detected in human breast milk and in the body fat of women (Kuruto-Niwa et al. 2007; Takeuchi et al. 2004). Although exposure doses of BPA measured in human tissues are lower than the maximum acceptable or reference dose of 0.05 milligram per kilogram body weight per day (IRIS 2011), animal studies appear to be showing a relationship between low doses of BPA and diseases such as prostate cancer (Wetherill et al. 2006), breast cancer (Jenkins and Lamartiniere 2009) and reproductive and developmental diseases (Newbold et al. 2007).

As of 2013, Canada, the US and the EC have banned the use of BPA in products used be infant children. It is worthwhile to note that their actions were not necessarily followed or fully supported by scientific evidence described above. In spite of a large amount of individual studies supporting BPA toxicity, its toxicity and health impacts are still perceived as inconclusive or uncertain. It was partly because a few but influential agencies in regulatory decision making process−Health Canada, the U.S. FDA and the European Food Safety Authority (EFSA)−have confirmed (and reconfirmed) the scientific conclusion that the current BPA exposure represents no significant risk to human health, including babies. Myer et al (2009) have raised doubts about the validity of the risk assessments conducted by the U.S. FDA and the EFSA. Myer et al. assessed that the decisions may have incorrectly reflected the current scientific conclusion over BPA toxicity as a result of overemphasizing outdated Good Laboratory Practices (GLP) and rejecting non-GLP studies. The uncertainty over BPA toxicity played a key role in banning BPA in baby products in Canada and the EU, which seek to establish environmental related regulations under precautionary principle. On the other hand, the U.S.'s recent decision to ban

BPA was made only after the industry voluntarily ceased to produce BPA-containing products and the American Chemistry Council representing plastic manufacturers filed a petition with the U.S. FDA requesting a ban on BPA. . Consumers can now purchase BPA-free plastic food and water containers in some countries, although the replacement chemical is not typically advertised. One of the alternatives, identified as Eastman Tritan^{TM} copolyester (ETC) has increasingly replaced BPA in many products (CQ Researcher 2010).

The Eastman Chemical Cooperation (Kingsport, Tennessee) introduced ETC in October 2007. Dimethyl terephthalate、2,2,4,4, tetramethyl-1,3-cyclobutanediol -1,4 cyclohexanedimethanol are components of ETC. Despite its growing use for the production of BPA-free consumer products, few independent risk assessment studies have been conducted on ETC. The evaluation of its safety has mainly relied on information provided voluntarily by the manufacturer, according to Material Safety Data Sheet (MSDS) or similar regulations that chemical manufacturers or importers shall develop a MSDS for chemicals they produce or import ETC is widely used to produce BPA-free products under no strict regulative control across the world. BPA and ETC perfectly capture the scenario where abundant information exists on the risk assessment of a controversial toxic chemical, whereas, little or no information exists on an alternative chemical that is gaining wide usage.

5. METHODS

We treat scientific conclusions and regulatory decisions as input parameters that capture the toxic risk of chemical substances. Accordingly, we define *risk* here as the outcome of combined scientific conclusions (empirical) and regulatory (conjectural) decisions about chemical toxicity. Empirical information is provided by sources varying authority or credibility,

including research published in peer-reviewed journals, private corporation literature, and governmental and non-governmental authorities.

First, we compare toxic risks between BPA and ETC. We combine BPA risk judgments (scientific conclusions) from authoritative organizations of Canada, the US and the EU who have had a major impact on laws and regulations for chemical substances worldwide. For ETC, we combine two professional judgments published in a peer-reviewed journal available as of July 2012 (Osimitz et al, 2012; Bittner & Yaniger, 2012). Table 3 presents (a) the summary of scientific conclusions used for this study, (b) their conversion to probability values and (c) credibility levels.

(c) reflects credibility levels weighted according to sources of information. We created credibility weights for different sources of data and treated them as degrees of belief. In this study, we grouped available information sources into three categories based on whether the information comes from a source that represents large international or global agencies (for example, the European Union's REACH program, assigned credibility weight of 0.75); national agencies (for example, the United State's National Toxicology Program, assigned a weight of 0.5) or State levels and small groups (e.g. peer-reviewed publications by individuals or scientific consensus of the State of California's Green Ribbon Science Panel assembled by the California Department of Toxic Substances Control, assigned a weight of 0.25). These credibility-weight assignments may also be viewed as the level of consensus required before publication of the information from particular agencies (see Table 4). The credibility weights were assigned for a temporary purpose in order to test the applicability of the proposed model. The credibility weights given to each type of information source represent important parameter values because they directly dictate the range, [*Bel*(t), *Pl*(t)]. Accordingly, credibility values can be modified

through systematic or empirical evaluations.

Another set of empirical information is regulatory decisions. Since regulatory decisions have not been established for ETC until today, instead, we compared the BPA regulatory decision status of Canada, the US and the EC at two different time points. Time A, (a) in Table 5, summarizes the regulatory decision status of the twenty-seven EU member countries and the fifty US states before the EC and the US declare BPA ban. For Time A, evidence on whether or not they or their (member) states passed a law banning the use of BPA was treated as representing the regulatory decision status. Time B, (b) in Table 5, reflects the current status of regulatory decisions. As of July 2012, they all have banned BPA use in baby products. The use of Time A is particularly important in that it would provide us with an opportunity to test the applicability of D-S theory in the ad-hoc period in regulatory decision making process.

The input parameters described above were combined using the D-S combination rule. We omit here a description of the calculation procedure. They are detailed in the supplementary materials. The next section discusses results.

6. RESULTS AND DISCUSSION

6.1 Results

Table 6 shows the finished calculation results and Figure 1 demonstrates the toxic risks of BPA and ETC resulting from combining the scientific conclusions. The lower the location of box, the lower the overall toxic risk. The narrower the box height is, the higher the result certainty.

The current degrees of belief [*Bel*(t)] in BPA and ETC are 0.034 and 0.097 respectively, implying that according to the current scientific opinion, BPA's perceived risk of being toxic is

0.034 whereas ETC's is 0.097. Uncertainty of the potential toxicity of ETC is not eliminated and the model results using D-S theory reflect this current status of investigations of ETC. The model generated two values, *Pl*(t) and the interval [*Bel*(t), *Pl*(t)], that indicates the possibility that ETC remains a potential toxicant pending verification by future studies. The plausibility value of ETC was 0.688. This value implies that, when adding new scientific conclusions, the ETC's maximum likelihood of being perceived as toxic by the scientific community may go up to 0.688 in the worst case scenario meaning that all other scientific conclusions support the proposition that ETC is toxic. On the other hand, the gap between *Bel*(t) and *Pl*(t) implies the magnitude of uncertainty about the risk estimates. The uncertainty in BPA's perceived toxicity is 0.216 and ETC is 0.591. This uncertainty reflects either a level of variation in scientific opinions or the uncertainty in sources of information. According to the result, uncertainty in ETC is greater than BPA. This result is consistent with the current situation of lacking information available on ETC risk assessment studies.

Figure 2 and Table 7 shows the results of combining the evidentiary weight of regulatory decisions made for BPA with the detailed values obtained through D-S theory-based model. We considered two different time windows in combining regulatory decisions. The column, Time A, calculates the status of the overall degree of belief on BPA toxicity taking into consideration regulatory decisions made by EU member states and states in the US before the EC and the US passed the law to ban BPA. The column, Time B, combines the current regulatory decision status that the Canadian government, the EC, and the U.S. have established.

The comparison at two different time frames demonstrates the changes of the degrees of belief on BPA toxicity before and after the regulatory decisions of the EC and the US. The degree of belief on BPA toxicity by the chemical regulatory community increased from 0.216 to

0.875. The uncertainty in this belief decreased from 0.409 to 0.063.

These results from the model are influential for salient circumstances. When scientific judgments and regulatory decisions remain conflicting (Time A), one can comprehend a low level of confidence in regarding BPA as a toxicant with considerable uncertainty. Prior to the regulatory decisions of the EC and the US, the degree of belief on BPA toxicity ($Bel(t)_{Time\ A}$) was 0.216 with an uncertainty range ($Pl(t)_{Time\ A} - Bel(t)_{Time\ A}$), 0.409. As of this writing, all the three regulatory entities−Canada, the US and the EC−, passed the law to ban BPA (Time B). Based on this information, one may intuitively come to the conclusion that BPA is a toxic chemical with a relatively low level of uncertainty. The results from our model were consistent with this intuition. The results reflecting the current status show the high level of confidence on BPA as a toxic chemical ($Bel(t)_{Time\ B} = 0.875$) with a narrow uncertainty range ($Pl(t)_{Time\ B} - Bel(t)_{Time\ B} = 0.063$). This comparison also highlights the significant gap between scientific conclusions and regulatory decisions concerning BPA. According to the results, the degrees of belief on BPA toxicity in the scientific community and the regulatory community are 0.034 and 0.875 respectively. 0.034 indicates a relatively very low level of concern that BPA might be a toxic substance compared with 0.875 in the regulatory community.

The different sets of evidence assembled for BPA (in Table 7) provides a range of intervals. This can be used for comparison of a chemical product against a proposed alternative. In the case of BPA and ETC, we see that consideration of the evidentiary value of regulatory decisions can increase the likelihood of considering BPA to be of higher toxicity than ETC especially with the body of evidence taken into account in Time B. This might create greater confidence in subsequent regulatory decisions. As importantly, the level of uncertainty, $Pl(A) - Bel(A)$, is seen to shrink as more evidence is taken into account. The implication of this is a

need to assemble more pieces of evidence for ETC in order to reduce the level of uncertainty associated with it.

6.2 Discussion

The results show how conflicting scientific views or regulatory decisions on a substance can be converted into a unified risk estimate without any loss of information and how this information can be used for comparison between substances which may have demonstrated substantial disparities in the quantity of evidence.

We discuss implications of the results in terms of D-S theory's strengths and limitations vis-à-vis risk assessment.

6.2.1 Strengths of the New Approach

The most significant strengths of D-S theory-informed model are its ability to:

(1) take into consideration the credibility (believability) of evidence, and

(2) take into consideration multiple lines or bodies of evidence.

Evidence tends to exhibit a certain level of uncertainty depending on credibility. However, the classic theory of probability and Bayesian theory ignore this uncertainty and the sum of the probabilities of each event resulting from an experimental model or an expert's subjective decision is assumed to equal one (P_{sum}= 1). In contrast, D-S theory makes allowance for this uncertainty (e.g., m_{sum}= 0.8, $m_{uncertainty}$= 0.2).

D-S theory can accept different subjective probabilities about model reliability through the employment of Dempster's rule of Combination. D-S theory also provides a mechanism for

combining several pieces of independent information. In contrast, conventional risk assessment procedures tend to select for the most conservative or credible piece of evidence and throw out the rest. Not only scientific opinions but also estimated risks obtained from different bioassays or epidemiological investigations tend to vary to some extent.

6.2.2 Limitations

The conversion of subjective scientific opinions into probability values is the most critical weakness that the current use of D-S theory presents. Although *Likert-type rating scales* have increasingly been used as a means of representing scientific opinions in an easy to understand manner, not only *Likert-type rating scales* being used in organizations differ from each other but also their rating scales have not necessarily been established in an incremental manner. Differently from the US NTP's use of a five-level scale to express their conclusions, the EU has classified reproductive toxicant into three classes. The classification from the SCF list contains toxicity concerns as well as data availability and levels in the SCF list do not always correspond with the degree of toxicity concern. It can cause the significant modification of the scale when converting the opinion into a probability value.

D-S theory presents a fundamentally novel approach to risk assessment. The underlying assumption of D-S theory is the view that the probabilities from the classic theory of probability or Bayesian theory tend to overestimate the probabilities as a result of ignoring evidence uncertainty. By taking into consideration evidence uncertainty, the probability value decreases (e.g., $P(a) = 0.5 \rightarrow Bel(A) = P(a) \times 0.8 = 0.4$, where 0.8 is the degree of belief about model selection). The combination process also contributes to the decrease in the probability value.

The probability value becomes lower as they are multiplied by other probability values in nature (e.g., $p(a)=1/2$, $p(b)=1/2 \rightarrow p(a) \times p(b) = \frac{1}{4}$). In contrast, conventional methodologies invariably select the highest unit risk estimate across various studies. This contrast between the two approaches points to the need to better define what the lowered estimates (emerging from D-S approach) mean. As it is, D-S theory-derived estimates cannot be simply compared to existing (conventionally derived) estimates for a compound because these numbers represent fundamentally different things. The most promising immediate application of our new approach is in the comparison of recognized toxicities between a compound and others (e.g., commercial substitutes).

6.2.3. Implications for Policy Making

The drawbacks of this new approach designed for the comparative risk assessment originate from the absence of two key institutional mechanisms rather than the unsuitability of the approach to risk assessment. In order to increase the confidence in outcomes from the new approach, the approach has need of two pieces of valid information; 1) well-defined toxicity scales translatable to probability values and 2) credibility scores of toxicity evaluation entities. They can be obtained through the development of two institutional mechanisms. They are as follows;

- Encourage the toxicity evaluation entities' effort to produce rigorous standardization in representing scientific opinions. The toxicity evaluation entities may consider refining their current toxicity scales in a unidirectional or incremental manner. It will make it easier to transfer scientific opinions into probability values.

- Establish a credit scoring system that evaluates the credibility of toxicity evaluation organizations. There are two possible approaches to obtain their credibility levels. Firstly, credibility rate can be scored through the conduct of survey that asks believability of toxicity evaluation entities directly to the general public. Credit scores can also be acquired through a longitudinal data analysis. Changes in scientific opinions over time which may reflect the lack of credibility can be counted and converted into probability values through statistics.

7. CONCLUSION

Despite the increasing use of scientific opinions in determining the toxicity of a controversial chemical, little progress has been made in effort to coordinate those different scientific opinions and provide a unified view toward the toxicity. The discrepancy contributes to prolongation of regulatory decision-making process related to chemicals from years to decades. This makes it difficult for chemical regulatory decision makers at multiple administrative levels to determine which evidence or opinion they should consider among controversial study results, scientific opinions and conflicting regulatory decisions. Those delayed decisions have contributed to prolonging the commercial use of potentially harmful chemicals resulting in that the public are being exposed to those chemicals for extended periods. Here, we developed a new risk assessment model that can combine different scientific opinions and regulatory decisions, and produce a unified risk estimate using D-S theory approach. The results from this model can serve as a useful guide for regulatory decision making on controversial chemicals. The simplified risk estimates from the model can be particularly useful to policy makers in developing countries that generally rely on international scientific expertise and prefer to await

final regulatory decisions of more affluent allied nations and multinational agencies. The results provide information on the perceived risks of controversial chemicals at the moment when the policy-makers need to render decisions. Based on the model output, some policy makers in developing countries may decide to ban BPA with reference to the current perceived toxicity risk in the regulatory community (*Bel*[t] = 0.875), whereas other countries may find insufficient reason to take action since the scientific community expressed a low level of concern over BPA toxicity (*Bel*[t] = 0.034). What this implies is that the results from our model can contribute to expedite regulatory decision making on controversial chemicals in many developing countries even during the ad-hoc period when final scientific judgments or regulatory decisions by the world leading entities remain incoherent. The international policy impact is that the strategy that we present may help phase out the use of potentially toxic chemicals in early stages of wide-spread distribution in developing countries.

We also demonstrated that the model can be used to compare the relative risk between toxic chemicals and proposed "greener" alternatives regardless of the differences in the amount of toxicological data available. While ETC has been considered as a safer substitute to BPA in commerce, the results from our D-S model indicate that ETC cannot be concluded to be safer than BPA until more studies are conducted. Based on this information, regulatory decision makers may postpone the approval of ETC as a safer alternative to BPA. It is also possible for regulatory policy makers to initiate targeted research programs in order to render more informed decisions.

Further studies are needed to extend the validity and reliability of the D-S model. For this research, we mainly focused on developing a novel risk assessment model using D-S theory and showing the applicability of the model to a real situation, the troubling case of BPA.

Although the current status of regulatory decisions and scientific opinions on BPA and ETC are interpreted adequately using the results from the model, further studies including testing the applicability of the model to other similar cases and comparing the results from the model to other similar risk assessment models results using objective measures are ongoing. We conclude that, the effective application of the model presented calls for two actions at the institutional level; 1) standardized scaling in representing scientific opinions and 2) a credit scoring system for chemical regulatory organizations.

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List of Figures

Figure 1. BPA vs. ETC: the comparison of toxicity risk in terms of scientific conclusions. The evidence set from Table 3 was combined using the D-S combination rule. The lower the location of box, the lower the overall toxic risks. The narrower the box height is, the higher the result certainty.

Figure 2. BPA toxicity risk change in terms of regulatory decisions. The evidence set from Table 5 was used to calculate BPA toxicity risk at two different time points, before and after the regulatory decisions of the EU and the US. The degree of belief on BPA toxicity by the chemical regulatory community increased from 0.216 to 0.875. The uncertainty in this belief decreased from 0.409 to 0.063.

[Tables]

Table 1. Comparison of Traditional Probability and Basic Probability Assignment

Power set of X, A owe^{x}	p(A)	*m*(A) (Degree of belief = 0.8)
Toxic	1.0	0.8
Non-toxic	0.0	0.0
Either (toxic or non-toxic)	0.0	0.2
Total	1.0	1.0

Table 2. Example of using Dempster's Combination Rule

		m_2 (C) Degree of belief = 0.6		
		Non-toxic (m=0.0)	Toxic (m=0.6)	Either (m=0.4)
m_1 (B) Degree of belief = 0.8	Non-toxic (m=0.0)	0.00	0.00	0.00
	Toxic (m=0.8)	0.00	0.48	0.32
	Either (m=0.2)	0.00	0.12	0.08

Table 3. Scientific Conclusions on BPA and ETC Toxicity as of 2012

	Canada	European Union	United States
(a) Scientific Conclusions	Safe (Health Canada)	Safe (EU REACH)	Some concern (US NTP)
(b) Toxic Risk (Converted from scientific conclusions)	0.0 [a]	0.0 [a]	0.5 [b]
(c) Source credibility (Degree of belief)	0.50	0.75	0.50

a. We have interpreted the scientific conclusion, 'safe', as a chance of being toxic equals zero.
b. U.S. NTP has used a five-level scale ranging from 'serious' to 'negligible', 'some concern' is located in the middle. So, we treated this conclusion as there is a 50 percent chance of being toxic.

(a) Bisphenol A

	Osimitz et al (2012)	Bitter and Yaniger (2012)
(a) Scientific Conclusions	Safe	Uncertain
(b) Toxic Risk (Converted from scientific conclusions)	0.0 [a]	0.5 [b]
(c) Source credibility (Degree of belief)	0.25	0.25

a. As we discussed before, we interpreted the scientific conclusion, 'safe', as a chance of being toxic equals zero.
b. Bitter and Yaniger (2012) states that Ostimitz et al's experimental approach is "debatable and /or incorrect" in several aspects and ETC' toxic risk is inconclusive. So we treat their professional opinion as 'uncertain'. We interpret it as there is a 50-50 chance.

(b) ETC

Table 4. Credibility Weights

Source	Credibility
Representative bodies of the scientific community at international (regional) level (e.g. EU)	0.75
Bodies of the scientific community at national level (e.g. US EPA)	0.50
Individual studies (e.g. Osimitz et al's study)	0.25

The quality and volume of evidence basing scientific opinions improve ↑

Table 5. Regulatory Decisions on BPA toxicity

	Canada	European Union [b]	United States [c]
(a) Regulatory Decision	Ban	- Ban (1/27) Non-toxic (8/27) Undecided (18/27)	- Ban (11/50) Non-toxic (0/50) Undecided (39/50)
(b) Toxic Risk (Converted from regulatory decision)	1.0 [a]	Toxic (1/27) Non-toxic (8/27) Either (18/27)	Toxic (11/50) Non-toxic (0/50) Either (39/50)
(c) Source credibility (Degree of belief)	0.5	-	-

a. Since the Canadian government declared BPA as a toxic substance, the chance of being toxic is regarded as one.
b. This summarizes the status of the regulatory decisions among E.U. member states before the E.C. announced Bisphenol A ban in baby products.
c. This summarizes the status of the regulatory decisions among states in U.S. before the U.S. Federal government announced Bisphenol A ban in baby products.

(a) Time A: Before EC and US make regulatory decisions

	Canada	European Union	United States
(a) Regulatory Decision	Ban (April, 2008)	Ban (January, 2011)	Ban(July, 2012)
(b) Toxic Risk (Converted from regulatory decisions)	1 [a]	1 [a]	1 [a]
(c) Source credibility (Degree of belief)	0.50	0.75	0.50

a. The action of banning the use of a toxic substance in any purpose is regarded as the statement that the substance is toxic for this study.

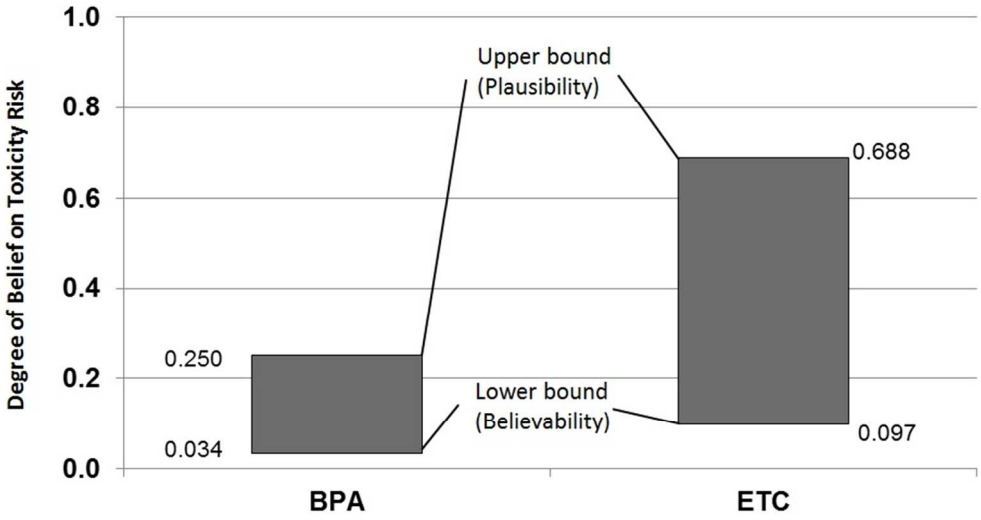
(b) Time B: July, 2012

Table 6. Results combining scientific conclusions using the D-S Based Risk Assessment Model

	BPA	**ETC**
Total Probability	[0, 1.0]	[0, 1.0]
k	0.094	0.031
$(1-k)$	0.906	0.969
m(t)	0.031	0.094
$\boldsymbol{Bel(t) = m(t)/(1-k)}$	**0.034**	**0.097**
Bel(f)	0.750	0.313
Pl(t) = 1 – Bel (f)	0.250	0.688
[*Bel*(t), *Pl*(t)]	**[0.034, 0.250]**	**[0.097, 0.688]**
Pl(t) − Bel(t)	0.216	0.591

Table 7. Results for BPA combining regulatory decisions using the D-S Based Risk Assessment Model

	Time A	**Time B**
Total Probability	[0.0,1.0]	[0, 1.0]
k	0.148	0.000
$(1-k)$	0.852	1.000
m(t)	0.184	0.875
$\boldsymbol{Bel(t) = m(t)/(1-k)}$	**0.216**	**0.875**
Bel(f)	0.376	0.063
$Pl(t) = 1 - Bel(f)$	0.624	0.938
[*Bel*(t), *Pl*(t)]	**[0.216, 0.624]**	**[0.875, 0.938]**
$Pl(t) - Bel(t)$	0.409	0.063



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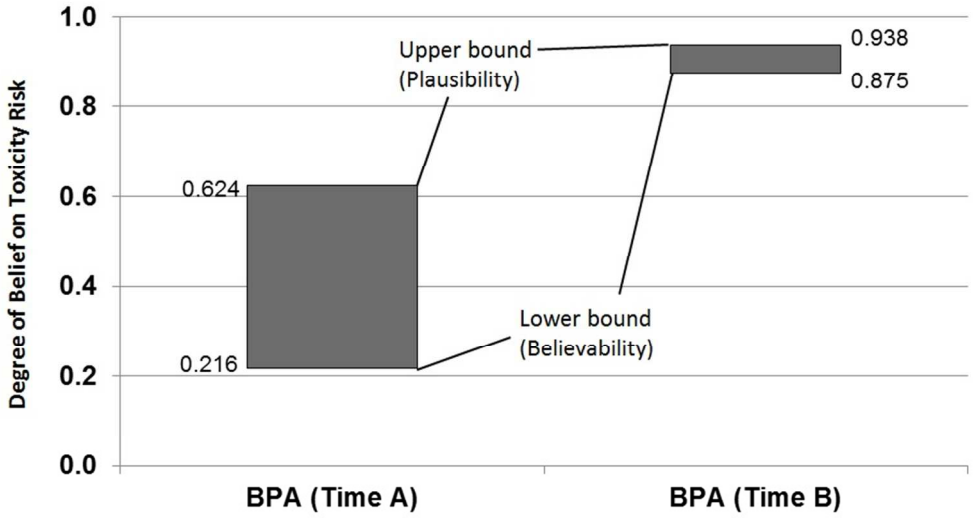

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