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Application of the draft NIOSH Occupational Exposure Banding Process to Bisphenol A: A case study

Cynthia J. Hines, **Thomas J. Lentz**, **Lauralynn McKernan**, **Pranav Rane**, **Christine Whittaker**

National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Cincinnati, Ohio

Abstract

Bisphenol A is a commercially important chemical used to make polycarbonate plastic, epoxy resins and other specialty products. Despite an extensive body of *in vitro*, animal and human observational studies on the effects of exposure to bisphenol A, no authoritative bodies in the U.S. have adopted or recommended occupational exposure limits for bisphenol A. In 2017, the National Institute for Occupational Safety and Health published a Draft process for assigning health-protective occupational exposure bands, i.e. an airborne concentration range, to chemicals lacking an occupational exposure limit. Occupational exposure banding is a systematic process that uses both quantitative and qualitative toxicity information on selected health effect endpoints to assign an occupational exposure band for a chemical. The Draft process proposes three methodological tiers of increasing complexity for assigning an occupational exposure band. We applied Tier 1 (based on the Globally Harmonized System of Classification and Labelling) and Tier 2 (based on authoritative sources/reviews) to assign an occupational exposure band to bisphenol A. Under both Tier 1 and 2, the occupational exposure band for bisphenol A was “E” (<0.01 mg/m^3), an assignment based on eye damage. “E” is the lowest exposure concentration range, reserved for chemicals with high potential toxicity. If eye damage was excluded in assigning an air concentration exposure range, then bisphenol A would band as “D” (>0.01 to 0.1 mg/m^3) under Tier 1 (based on reproductive toxicity and respiratory/skin sensitization) and under Tier 2 (based on specific target organ toxicity-repeated exposure). In summary, Tiers 1 and 2 gave the same occupational exposure band for bisphenol A when eye damage was included (“E”) or excluded (“D”) as an endpoint.

Keywords

BPA; Bisphenol A; GHS; hazard evaluation; occupational exposure banding

Corresponding Author: Thomas J. Lentz, tlentz@cdc.gov, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, 1090 Tusculum Ave, Cincinnati, OH 45226.

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INTRODUCTION

Bisphenol A (BPA) (CAS 80-05-7) is a commercially important chemical used to make polycarbonate plastic, epoxy resins and other specialty products. At room temperature, BPA is a white solid prill (dry sphere) or a flake. Research exploring the response of biological systems to BPA, including *in vitro*, laboratory animal and human observational studies, has been extensive.[1–7] In particular, over the past decade studies have emerged describing occupational exposures to BPA and its potential effects on workers.[8–12] Despite this growing body of literature, occupational exposure limits (OELs) for BPA are few and have been adopted or recommended mainly in Europe.[13–14] In the United States, no authoritative bodies have adopted or recommended OELs for BPA in air or biological matrices.

Thousands of chemicals in commerce, with varying levels of information on toxicity, do not have OELs. Nonetheless, occupational safety and health (OS&H) professionals must manage any risks that these chemicals may pose to workers. To manage risk from inhalation exposure, OS&H professionals need a target air concentration or concentration range that triggers risk management requirements, including the design, installation and operation of engineering controls and the selection of appropriate respiratory protection. The connection between target air concentration and degree of control (engineering, respiratory or other control) is central to controlling worker exposures.

In the absence of OELs established by authoritative organizations, other groups and individuals have developed approaches to describe health-protective occupational exposure (or hazard) bands.[15–19] With the exception of Arnone et al.,[18] these approaches link an exposure band to an air concentration range. Recognizing the need for a practitioner-oriented process for developing exposure bands, the National Institute for Occupational Safety and Health (NIOSH) issued draft guidance on an occupational exposure banding process for evaluating chemical hazards.[20]

Occupational exposure banding is a systematic process that uses both quantitative and qualitative toxicity information on selected health effect endpoints to assign a health-protective occupational exposure band (OEB) to a given chemical. Under the Draft NIOSH Occupational Exposure Banding process, an OEB is an air concentration range. The OEB serves as starting point for risk management decisions.

The Draft NIOSH Occupational Exposure Banding process has three Tiers (1, 2 and 3) of increasing complexity.[20] Underpinning all Tiers is quantitative and/or qualitative information on the substance's toxicity. Tier 1 relies on the Globally Harmonized System of Classification and Labelling (GHS) hazard codes/statements for eight health effect endpoints to assign an OEB.[21] Tier 2 relies on quantitative and qualitative information from authoritative sources and reviews for nine health effect endpoints to assign an OEB. Tier 2 requires an understanding of toxicology and is substantially more involved than Tier 1. Tier 3 entails performing a comprehensive quantitative risk assessment in order to assign an OEB and requires specialized knowledge in toxicology and risk assessment.

Our objective here is to apply Tiers 1 and 2 of the Draft NIOSH Occupational Exposure Banding process to BPA as a case study. In doing so, we examine and comment on decisions and issues that arise as part of the exposure banding process.

METHODS

We applied Tiers 1 and 2 of the Draft NIOSH Occupational Exposure Banding process to assign an OEB for BPA. For both Tiers, we assigned an exposure band ranging from A to E to each health effect endpoint, (herein referred to as an "endpoint exposure band") using criteria specific to the Tier (Supplemental Tables S1–S10). Each endpoint exposure band represents an order of magnitude decrease in an airborne concentration range with "A" the highest concentration range and "E" the lowest concentration range (Table 1). Airborne particles have different concentration ranges than gases and vapors.

In the Tier 1 assessment of BPA, we relied on GHS hazard codes in the GESTIS substance database to assign an endpoint exposure band to the eight Tier 1 endpoints (Table 2).[14] NIOSH selected these eight endpoints for consistency with the GHS endpoints. For Tier 1, we also checked the GHS hazard codes in the Annex VI database that is part of the Classification, Labelling, and Packaging (CLP) regulation within the European Union.[22]

In the Tier 2 assessment of BPA, we relied on several authoritative reviews and databases to assign endpoint exposure bands to nine health endpoints (Table 3). The nine Tier 2 endpoints differ from the eight Tier 1 endpoints in that in Tier 2, respiratory sensitization and skin sensitization are separate endpoints and the germ cell mutagenicity endpoint expands to the more comprehensive category of genotoxicity. NIOSH specified endpoint-specific criteria for the data to be included in (or excluded from) a Tier 2 assessment (Table 4).

In the Draft NIOSH Occupational Exposure Banding process, NIOSH classifies sources of authoritative reviews/data used in Tier 2 for each endpoint as either Rank 1 (preferred) or Rank 2 (second-level) sources, with Rank 2 sources used only if Rank 1 sources have no endpoint information. Tier 2 also includes a measure of data availability/adequacy for each endpoint referred to as the "endpoint determinant score" (EDS), which is a weighted score indicating the presence/absence of data for banding a specific health endpoint. An EDS greater than zero indicates that the available data are sufficient to assign an endpoint exposure band. The EDS value varies by endpoint, with greater weight (higher EDS) given to endpoints typically associated with chronic exposure compared to endpoints typically associated with short-term exposure (Supplemental Table S11). The sum of the EDSs across all nine endpoints yields a "total determinant score" (TDS). NIOSH considers a TDS of at least 30 sufficient to assign an OEB for the chemical under Tier 2.

The endpoint band with the lowest exposure concentration range within a Tier becomes the Tier-specific OEB (e.g. "Band E" has a lower exposure concentration range than "Band D"). A chemical could have different OEBs assigned under Tiers 1 and 2. We did not conduct a Tier 3 assessment of BPA because our focus for this case study was on the Tier 1 and 2 assessment processes that OS&H professionals are most likely to perform.

RESULTS

Tier 1

Under Tier 1, GHS hazard codes were available in GESTIS for three of eight endpoints (Table 2). Assigned endpoint exposure bands were “E” for eye damage/irritation, “D” for respiratory/skin sensitization and “D” for reproductive toxicity (Table 2). Therefore, the OEB for BPA assigned under Tier 1 was “E” (<0.01 mg/m^3), the endpoint band with the lowest exposure concentration range (based on eye damage/irritation) of the three endpoints with GHS hazard codes. If eye damage was excluded as an endpoint for banding an air concentration, then the OEB for BPA under Tier 1 would be “D” (>0.01 to 0.1 mg/m^3) based on respiratory/skin sensitization and reproductive toxicity (Table 2). GHS hazard codes for BPA were the same in the Annex VI and GESTIS databases. The Draft NIOSH banding process does not use one of the GHS hazard codes for BPA (H335, respiratory irritation). The H335 hazard code for BPA is based on data that suggests BPA has a limited potential for respiratory irritation.[23]

Tier 2

Endpoint banding results under Tier 2 are in Table 3. The Tier 2 TDS was 85, indicating sufficient data to assign an OEB. For two of the nine Tier 2 endpoints, no data (respiratory sensitization) or authoritative reviews (cancer) were available. Endpoint-specific exposure bands were “A” for acute toxicity, skin corrosion/irritation, genotoxicity and skin sensitization, “C” for reproductive toxicity (only studies performed under Good Laboratory Practices (GLP) considered), “D” for specific target organ toxicity – repeated exposure, and “E” for eye damage.

For the reproductive toxicity endpoint, NIOSH recommends using NOAELs derived from studies performed under internationally accepted test guidelines, often referred to as “GLP studies”.[24–26] If non-GLP studies that were considered “adequate and of high/useful utility” in the 2008 National Toxicology Program (NTP) review of BPA had been included in the reproductive toxicity endpoint evaluation, the reproductive endpoint would have been assigned an endpoint band of “E”.[5] NTP relied on the scientific judgment of its expert panel members to assess the utility of studies under consideration.[27]

The skin sensitization endpoint considers both quantitative (e.g. local lymph node assay tests) and qualitative data (e.g. NIOSH SK-SEN notation).[28] Both quantitative and qualitative skin sensitization data were available for BPA, with an endpoint band of “A” for the quantitative data, and “E” for the qualitative data. In the Draft NIOSH banding process for the skin sensitization endpoint, quantitative data takes precedence over qualitative data, thus the skin sensitization endpoint banded as “A”.

The OEB for BPA assigned under Tier 2 was therefore “E” (<0.01 mg/m^3), the endpoint band with the lowest exposure concentration range (based on eye damage) of the nine endpoints evaluated. If the reproductive toxicity endpoint included non-GLP studies deemed “adequate and of high/useful utility” in the 2008 NTP review[5], then the reproductive toxicity endpoint would also support an OEB of “E”. If eye damage was excluded as an endpoint for

an air concentration OEB, then the OEB for BPA under Tier 2 would be “D” (>0.01 to 0.1 mg/m^3) based on the specific target organ toxicity-repeated exposure endpoint.

DISCUSSION

We used the Draft NIOSH Occupational Exposure Banding process to identify a target air concentration OEB for worker exposure to BPA. We conducted this effort as a case study of applying the Draft NIOSH banding process to a chemical with substantial commercial use, documented worker exposure,[29–30] but no U.S. OELs. Under both Tier 1 (based on GHS hazard codes) and Tier 2 (based on authoritative sources/reviews), the OEB was “E”, representing an air concentration of ≤0.01 mg/m^3. The health effect basis for an “E” band in both Tiers was serious eye damage/irritation.

We compared endpoint bands assigned under both Tiers. Two of three endpoint bands assigned in Tier 1 differed from those assigned in Tier 2. In Tier 1, respiratory/skin sensitization had an endpoint band of “D” (based on potential for skin sensitization from case reports), but an endpoint of “A” in Tier 2 where quantitative data (e.g. local lymph node assay tests) took precedence over qualitative data (e.g. case reports). The reproductive toxicity endpoint band also differed between Tier 1 (“D”) and Tier 2 (“C” for GLP studies; “E” for non-GLP studies). We could not compare remaining endpoints because GHS codes were available for only three Tier 1 endpoints.

The Draft NIOSH occupational exposure banding guidance indicates that a Tier 2 assessment is optional if a Tier 1 assessment results in an OEB of “E”, the rationale being that “E” already represents the lowest air concentration range. NIOSH notes, however, that a Tier 2 evaluation could be beneficial if detailed chemical information identified in Tier 2 results in a re-consideration of the appropriate OEB. For BPA, even though we had more detailed information in Tier 2 for several endpoints, the OEB remained at “E” as in Tier 1 because the potential for serious eye damage triggered in Tier 2 the lowest exposure concentration range (endpoint band “E”).

The OEB assignment for BPA under both Tiers relied on an endpoint (eye damage/irritation) not typically associated with inhalation exposure. If the eye damage/irritation endpoint was excluded, then BPA would band as “D” (>0.01 to 0.1 $mg/^3$) under Tier 1 based on respiratory/skin sensitization and reproductive toxicity, and as “D” under Tier 2 based on specific target organ toxicity-repeated exposure. Thus, under both Tiers, a higher exposure range would apply after excluding the eye endpoint. A relationship may sometimes exist between eye irritation severity and an air concentration, for example, acid mists such as acetic and formic acid.[31–32] For solid materials, such as powders, flakes, granules, etc., such a relationship may be less clear. BPA has a limited potential for respiratory irritation,[23] an effect that might have a relationship with an air concentration OEB; however, the Draft NIOSH Occupational Exposure Banding process does not include respiratory irritation in Tiers 1 or 2.

This case study also illustrated the impact of using only GLP studies when evaluating the reproductive toxicity endpoint under Tier 2. When restricted to GLP studies, the

reproductive toxicity endpoint for BPA banded as “C”, whereas when other “high/useful utility” studies as evaluated by NTP were included,[5] the endpoint banded as “E”, a factor of 100 difference in the banded air concentration. GLP studies are few among the many animal studies examining reproductive endpoints for BPA. Users might consider including non-GLP studies to enrich the amount of available data, particularly if an authoritative body has reviewed and evaluated the non-GLP studies.

Assignment of an appropriately protective OEB is dependent on GHS hazard codes (Tier 1) or authoritative sources/reviews (Tier 2), sources that presumably reflect current understanding of a chemical’s toxicity. A limitation of both Tier 1 and Tier 2 is the degree to which GHS hazard codes and authoritative sources/reviews are updated as new data become available. Both the designation of GHS hazard codes and the issuance of authoritative reviews require an evaluation process that can be lengthy and not necessarily compelled by law or regulation. GHS and authoritative source reviews of new toxicity data may occur infrequently, particularly for chemicals requiring an in-depth evaluation.

For chemicals with a substantial amount of new data not reviewed under GHS or by authoritative sources, a Tier 3 comprehensive risk assessment might be appropriate. BPA may be a candidate for a Tier 3 assessment. The Tier 2 assessment of the reproductive health endpoint for BPA relied heavily on an authoritative source review published by NTP in 2008.[5] In the decade since the review, published research on BPA reproductive and developmental toxicity has grown considerably and important additional research is forthcoming.[33] The European Chemicals Agency, another authoritative source used in the Tier 2 assessment, last published a review of BPA in 2010.[23]

In conducting this case study of BPA, we also informally assessed the effort and knowledge needed to conduct a Tier 1 and Tier 2 assessment by an experienced, certified industrial hygienist (author CJH). Assigning an OEB for BPA under Tier 1 was straightforward and most OS&H professionals should be able to conduct a Tier 1 assessment easily. The effort and knowledge needed to complete Tier 2 varied by endpoint for BPA. The reproductive toxicity endpoint had the most data to review under the Draft NIOSH Occupational Exposure Banding guidelines and was the most time consuming of the endpoints to assess. Studies with no observable adverse effects levels (NOAELs) for the reproductive toxicity endpoint were numerous and the effects diverse (Table 3). The Draft NIOSH Occupational Exposure Banding process weights NOAELs for all effects equally (i.e. a particular effect is not considered more or less important than another effect). For some studies, including some GLP studies, the reported NOAELs could not be used because the NOAEL was expressed as “greater than” a certain value. Such values are not used in the Draft NIOSH banding process.

A Tier 2 assessment clearly has a learning curve. The user needs to become familiar with the NIOSH banding process, data sources and documentation steps. Depending on the amount of data available for each Tier 2 endpoint and taking into consideration other time commitments, a novice user may need several days to access sources, compile relevant data, assess data adequacy, and complete the banding of all endpoints. Training in advance on the Draft NIOSH Occupational Exposure Banding process would likely expedite the process. A Tier 2 assessment requires a basic understanding of toxicology. Access to an

experienced toxicologist for guidance would be highly desirable. In Tier 2, the process of identifying relevant endpoint data has the added benefit of illuminating endpoints with little toxicity data or lacking authoritative reviews. In the case of BPA, we found no authoritative reviews for the carcinogenicity endpoint and no data were available to evaluate the respiratory sensitization potential of BPA. An ancillary benefit to the user conducting a Tier 2 assessment is a greater familiarity with a chemical's toxicity.

The Draft NIOSH guidance does not assign an averaging time (e.g. 8hr, 10hr, 15 min) to an OEB. Rather, a person applying the OEB in practice would need to decide on an exposure duration appropriate for the chemical of interest. For substances such as BPA that are not acutely toxic, a longer averaging time may be appropriate. Shift length might also be considered when applying an OEB. For example, long shift lengths (e.g. 12-hr) are common in the chemical industry. For chemicals that have an OEB with an associated air concentration range (i.e. OEBs A to D), one might use the low end of the range as a target air concentration.

CONCLUSION

Sufficient information was available to apply the Draft NIOSH Occupational Exposure Banding process to BPA as a case study. GHS hazard statements were available under Tier 1 and adequate data were available for seven of nine endpoints under Tier 2. Under both Tier 1 and Tier 2, the OEB for BPA was "E" (<0.01 mg/m^3), an assignment driven by eye damage. If eye damage was not used in assigning an air concentration exposure range, then under both Tiers the OEB for BPA would be "D" (>0.01 to 0.1 mg/m^3). The Draft NIOSH Occupational Exposure Banding process is a resource for OS&H professionals to guide risk management and exposure control decisions. An OEB derived from applying this process, including for BPA, however, is voluntary and not a NIOSH recommendation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Airborne concentration ranges associated with Draft NIOSH Occupational Exposure Bands.

Occupational Exposure Band	Airborne Target Range	
	Particles (mg/m^3)	Gas or Vapors (ppm)
A	>10	>100
B	>1 to 10	>10 to 100
C	>0.1 to 1	>1 to 10
D	>0.01 to 0.1	>0.1 to 1 ppm
E	≤0.01	≤0.1

Table 2.

Tier 1: Occupational exposure banding results for BPA under Draft NIOSH Occupational Exposure Banding process.

Endpoint	Hazard Code*	Hazard Category	Hazard Statement	Endpoint Band
Acute Toxicity	None			
Skin Corrosion/Irritation	None			
Eye Damage/Irritation	H318	1	Causes serious eye damage	E
Respiratory and Skin Sensitization	H317	1	May cause an allergic skin reaction	D
Germ Cell Mutagenicity	None			
Carcinogenicity	None			
Reproductive Toxicity	H360F	1B	Suspected of damaging fertility	D
Specific Target Organ Toxicity – Repeated Exposure	None			

Table 3.

Tier 2: Occupational exposure banding results for BPA under Draft NIOSH Occupational Exposure Banding Process.

Endpoint	Data Source (Rank)	Reference	Health Effect		Endpoint Band	Endpoint Band with Lowest Conc. Range	EDS
Acute Toxicity			Species	LD_{50}, mg/kg			
	ChemID*plus* (1)	NIH (2017)[A]	Guinea pig, oral	4000	A		
			Mouse, oral	2400	A		
			Rabbit, oral	2230	A		
			Rat, oral	3250	A		
	HSDB (2)	NIH (2017)[B]	Rat, oral	5000	A	A	5
			Rat, oral	male 4100	A		
				female 3300	A		
			Mouse, oral	male 5200	A		
				female 4100	A		
			Mouse, oral	2500	A		
Skin Corrosion/Irritation	NIOSH SK Profiles (1)	NIOSH (2011)	Non-irritating		A	A	5
	REACH (1)	ECHA (2010)	Non-irritating		A		
Eye Damage/Irritation	REACH (1)	ECHA (2010)	Serious Eye Damage			E	5
Respiratory Sensitization	No data	NA	NA		NA	NA	0
Skin Sensitization	*Quantitative*						
	REACH (1)	ECHA (2011)[C]	Modified LLNA: Not sensitizing		A		
	NIOSH SK Profiles (1)	NIOSH (2011)	Modified LLNA: Not sensitizing		A	A (based on quantitative data)	5
	Qualitative						
	NIOSH SK Profiles (1)	NIOSH (2011)	Case reports: Skin sensitizer, photoallergen		E		
Genotoxicity	NTP (1)	NTP (2008)	Negative Results		A		
	WHO-ICPS (1)		Negative Results		A	A	5
	REACH (1)		Negative Results		A		

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Endpoint	Data Source (Rank)	Reference	Health Effect		Endpoint Band	Endpoint Band with Lowest Conc. Range	EDS
Carcinogenicity	No authoritative reviews	NA	NA		NA	NA	0
Reproductive Toxicity			*GLP Studies*				
			Lowest endpoint effect			GLP Studies Only C	
	NTP (1)	NTP (2008)	NOAEL,	mg/kg/day			
			Developmental		C		
			Rat, oral	4.75	A		
			Mouse, oral	1000	C		
			Mouse, oral	5		Adequate & High or Useful Utility Included E	30
			Multigeneration		C		
			Rat, oral	4.75	A		
			Mouse, oral	840	C		
			Mouse, oral	30	A		
			Mouse, oral	437.5			
			Adequate & High or Useful Utility Studies				
			All of the above studies plus,				
			Developmental				
			Rat, oral	100	B		
			Rat, oral	0.1	E		
			Rat, oral	0.1	E		
			Mouse, oral	1000	A		
			Mouse, oral	0.002	E		
			Reproductive-Female				
			Rat, oral	0.004[D]	E		
			Reproductive-Male				
			Rat, oral	200	B		
			Rat, oral	11.846	C		
			Rat, oral	200	B		
	Health Canada (1)	Health Canada (2008)[E]	Developmental				

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Endpoint	Data Source (Rank)	Reference	Health Effect		Endpoint Band	Endpoint Band with Lowest Conc. Range	EDS
			Rat, oral	0.01[F]	E		
			Mouse, oral	0.001[G]	E		
			Mouse, oral	0.002	E		
			Rat, oral	0.004[H]	E		
			Rat, oral	0.25[I]	E		
			Species, route	NOAEL			
Specific Target Organ Toxicity – Repeated Exposure	IRIS (1)	U.S. EPA[J]	Rat, oral, 103 weeks	5[K] mg/kg/day	D		
	REACH (2)	ECHA (2010)	Mouse, oral, two generation	50 mg/kg/day	C	D	30
			Rat, inhalation, 13-weeks	10,000 μg/m^3	B		
						TDS	85

Abbreviations: **Conc:** concentration; **EDS:** endpoint determinant score; **LLNA:** localized lymph node assay; **NA:** Not Applicable; **NTP:** National Toxicology Program; **REACH:** Registration, Evaluation, Authorisation, and Restriction of Chemicals; **TDS:** total determinant score; **WHO-IPCS:** World Health Organization: International Programme on Chemical Safety

[A] National Institutes of Health (NIH): ChemIDplus: Bisphenol A. U.S. National Library of Medicine, Bethesda, MD, 2017. Available at https://chem.nlm.nih.gov/chemidplus/rn/80-05-7 (accessed 17 Aug 2018).

[B] National Institutes of Health (NIH): HSDB (Hazardous Substances Database): Bisphenol A. U.S. National Library of Medicine, Bethesda, MD, 2017. Available at https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~YYboC0:1 (accessed 17 Aug 2018).

[C] European Chemicals Agency (ECHA): "4,4'-Isopropylidenediphenol (Bisphenol A. Additional Information on REACH Registration Dossier, European Commission, Luxembourg, 2011." Available at http://www.reachcentrum.eu/Consortia%20Documents/P-I209/Other/P-I209_EC201-245-8_Information_Registration_%202011.10.20.pdf (accessed 18 Aug 2017).

[D] Estimated from LOAEL of 0.04 mg/kg/day

[E] Health Canada: Health Risk Assessment of Bisphenol A from Food Packaging Applications. Bureau of Chemical Safety, Food Directorate, Health Products and Food Branch. Ottawa, Canada, 2008." Available at http://www.hc-sc.gc.ca/fn-an/alt_formats/hpfb-dgpsa/pdf/securit/bpa_hra-ers-eng.pdf (accessed 17 Aug 2018).

[F] Estimated from LOAEL of 0.1 mg/kg/day

[G] Estimated from LOAEL of 0.01 mg/kg/day

[H] Estimated from LOAEL of 0.04 mg/kg/day

[I] Estimated from LOAEL of 2.5 mg/kg/day

[J] United States Environmental Protection Agency (EPA): Integrated Risk Information System. Bisphenol A, 2017. Available at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0356_summary.pdf (accessed 16 Aug 2018).

[K] Estimated from LOAEL of 50 mg/kg/day

Table 4.

Data selection criteria for Tier 2 under DRAFT NIOSH Occupational Exposure Banding Process.

Endpoint	Tier 2 Data Selection Criteria
Acute Toxicity	1. Acute lethality data expressed as LD_{50} or LC_{50} 2. Routine experimental animals, e.g. rats, mice, rabbits, guinea pigs etc. Exclude chickens, frogs, etc. 3. Route of administration: oral, dermal or inhalation. Exclude subcutaneous, intraperitoneal, intravascular routes 4. Single dose. Exclude multiple dose studies. 5. Exclude inhalation studies where exposure duration not reported. If exposure duration other than four hours, adjust LC_{50} using ten Berge equation (NIOSH 2017, Table 3–21) 6. Exclude LD_{50} or LC_{50} values preceded by a greater than (>) symbol. 7. Exclude LD_{50} or LC_{50} values presented as a range of concentrations when values in the range fall within occupational exposure bands B-E, except when the range reports values separately for male and female, in which case the low end of range is used for banding.
Skin Corrosion/ Irritation	1. Assessment from authoritative organizations or authoritative reviews 2. Assessment based on a chemical in its pure form unless exposure banding targeted at a specific product with diluted or non-concentrated chemical.
Eye Damage/ Irritation	1. Assessment based on authoritative reviews
Respiratory Sensitization	1. Assessment based on authoritative reviews
Skin Sensitization	Qualitative 1. Human patch testing for sensitization Quantitative 1. LLNA EC3 2. GMPT 3. Buehler guinea pig test
Genotoxicity	1. Assessment based on authoritative reviews
Carcinogenicity	Quantitative 1. Potency information: slope factor, inhalation risk unit, tumorigenic dose (TD_{05}) or concentration (TC05)[A] Qualitative 1. Assessment based on authoritative reviews
Reproductive Toxicity	1. Internationally-accepted test guideline (i.e. GLP or OECD) studies preferred 2. NOAEL, BMDL or BMCL values that assess: a) Developmental toxicity b) Perinatal and postnatal toxicity c) One-generation or two generation toxicity d) Reproductive/developmental toxicity e) Combined repeated dose toxicity study with reproductive/developmental toxicity f) Short- or long-term repeated dose toxicity (i.e. impairment of reproductive function in the absence of significant generalized toxicity) 3. If no NOAEL or BMDL values are available, use LOAEL, if available, divided by 10 to estimate a NOAEL equivalent.
Specific Target Organ Toxicity – Repeated Exposure	1. NOAEL or BMDL value from a study of at least 28 days. 2. If study duration 90 days or longer, reported NOAEL or BMDL is used. 3. If study duration ≥28 days but less than 90 days, NOAEL is divided by 3 to estimate a 90-day equivalent NOAEL. 4. If no NOAEL or BMDL values are available, use LOAEL, if available, divided by 10 to estimate a NOAEL equivalent. 5. If multiple NOAELs or BMDLs are available for an exposure route, use the lowest route-specific value.

BMCL: Benchmark concentration lower bound; **BMDL:** benchmark dose lower bound; **GLP:** good laboratory practices; **GPMT:** guinea pig maximization test; **LC_{50}:** lethal concentration 50%; **LD_{50}:** lethal dose 50%; **LLNA EC3**: local lymph node assay effective concentration required to produce a three-fold increase in the stimulation index compared to vehicle-treated controls; **LOAEL:** lowest adverse effect level; **NOAEL:** no observable adverse effect level; **OECD:** Organisation for Economic Cooperation and Development

[A]Associated with a 5% increase in tumor incidence or mortality