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Review

Assessing the toxicity of polymeric food-contact substances ☆

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ABSTRACT

The US Food and Drug Administration's Office of Food Additive Safety in the Center for Food Safety and Applied Nutrition conducts safety assessments of food additives, including food-contact substances such as polymeric and oligomeric materials that have the potential to migrate to food. Traditionally, little toxicity testing has been conducted on the low-molecular weight oligomeric fraction (<1000 Da) of these food-contact substances. At lower exposures (⩽150 μg/person/day), safety has been assessed based on the use of toxicity data on the monomeric components of these polymers as a sufficiently conservative approach for addressing the concern for genetic toxicity and carcinogenicity of the low-molecular weight oligomers (LMWOs). This paper discusses this assumption relative to the available data on these substances and their monomeric components in the context of exposures of ⩽150 μg/person/day with emphasis on the evaluation of the potential genetic toxicity of these compounds. In most instances, data are available on either the monomers or the monomers' structural class to conservatively address the potential genetic toxicity of the LMWOs. Caveats to this generalization are also discussed. The assessment of LMWOs is important because they can be one of the primary migrants to food from a polymeric food-contact substance.

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1. Introduction

The Federal Food, Drug, and Cosmetic Act, as amended (the Act), provides the US Food and Drug Administration (FDA) with the authority to perform a pre-market safety evaluation of food additives. The Act requires manufacturers to demonstrate the safety of food additives before marketing. Food additives are defined as any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component of or otherwise affecting the characteristics of any food, unless the material is generally recognized as safe (GRAS) or prior-sanctioned for the use. The general safety requirements for indirect food additives, including food-contact substances, are codified in the US Code of Federal Regulations (CFR) Title 21. A food-contact substance (FCS) is defined as any substance that is intended for use as a component of materials used in manufacturing,

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packing, packaging, transporting, or holding food if such use is not intended to have any technical effect in the food (Section 409(h)(6) of the Act). The Act defines the general safety standard for evaluating a food additive as: "...proof of a reasonable certainty that no harm will result from the intended use of an additive." In prescribing this standard, the US Congress recognized that absolute safety of any substance can never be proven, considering the fact that virtually any material administered in sufficiently high doses will elicit some toxicity. Within FDA's Center for Food Safety and Applied Nutrition, the Office of Food Additive Safety (OFAS) is responsible for premarket evaluation of food and color additives submitted in petitions and notifications, and for the evaluation of GRAS notifications. The 1997 Food and Drug Administration Modernization Act amended the Act to institute the premarket notification system for FCSs, currently the primary regulatory process for evaluating the safety of FCSs.

In evaluating human exposure to a FCS, OFAS considers the quantity of the FCS and any of its impurities that migrate to food, the fraction of the daily diet that contacts the FCS, and the fraction of all food contacting the FCS that is aqueous, acidic, alcoholic and fatty food packaged in the FCS to obtain an estimated daily intake (EDI) of the FCS and any impurities.[1] Based on this approach, OFAS has outlined a tiered toxicity testing strategy for assessing the potential toxicity of the FCS and its impurities.[2] OFAS generally recommends that the test substance used for safety studies be identical to the substance that is expected to migrate to food. Ordinarily, the appropriate test substance is the FCS itself, or the impurities, unless the FCS or impurity is demonstrated to decompose under the intended conditions of use. In such a case, the decomposition products are evaluated under the same safety paradigm. In this way, performance of toxicity assays is straightforward as the test substance can be obtained rather easily either through manufacturing or suppliers. However, if the FCS is a polymer, OFAS recommends toxicity testing on the low-molecular weight oligomers (LMWOs; typically $\leqslant$1000 Da with exceptions for fluorinated compounds) but not on the polymer itself, as the oligomers are expected to be the primary migrants to food from use of the FCS. In addition, due to their smaller size relative to a polymer, oligomers are considered to be more biologically relevant than polymers because of expected absorption limitations for the polymer (Donovan et al., 1990). In this regard, OFAS' approach to polymers is rather unique.

Since the inception of FDA's food-contact notification (FCN) program, OFAS has emphasized genetic toxicity assays as a first tier screening tool for potential carcinogens. OFAS' tiered testing recommendations centers on the generalization that carcinogenicity is the most sensitive endpoint. As discussed below, the availability of other data or concerns based on structure–activity relationships (SAR) might suggest additional toxicity tests to ensure the safe use of a FCS. The recommendation to conduct these assays occurs at the exposure range of 1.5–150 μg/p/d, unless structural alerts or other information suggests an alternative approach. Although OFAS does not require testing below 1.5 μg/p/d, publicly-available data regarding the toxicity of a substance is considered at any exposure level (i.e., even below 1.5 μg/p/d). Based on a review of the current inventory of FCNs, the majority of exposures to FCSs and their impurities are $\leqslant$150 μg/p/d. Accordingly, the data necessary to support the safety of LMWOs usually consist of a literature search focusing on the potential toxicity of the material and two genetic toxicity assays. While the recommended tests are in vitro, making them less costly than in vivo toxicity assays, it may be difficult and costly for the submitter to obtain sufficient amounts of LMWOs to conduct the recommended toxicity assays for ensuring the safe use of their product. As such, since the inception of the genetic toxicity recommendations, submitters have presented arguments that the toxicological data (typically genetic toxicity and carcinogenicity data) on the monomer is sufficient to support the safety of the LMWOs, stating that in most cases the structurally alerting feature is consumed in the polymerization, for example as with polystyrene. In the absence of data to suggest that this alternative approach is non-protective, OFAS has concurred with the submitter in cases where the dietary exposures are $\leqslant$150 μg/p/d and no other information is available to suggest additional concerns. The case by case conclusions are based on the underlying assumption that the LMWOs are less toxic than any of the individual monomeric components due to the participation of the monomer's reactive groups in the polymerization. Typically, the results of genetic toxicity assays provided to OFAS for product submissions are predominately concluded to be negative. This skewing of data is a common problem in the publicly-available food additive data inventory as most compounds reaching the stage of the approval process may be triaged by inexpensive in vitro genetic toxicity assays leading to additional development of product approval candidates. As such, for compounds producing positive results, the data may remain confidential as it is either not submitted to the agency or did not reach approval status. Alternatively, when positive in vitro genetic toxicity studies are submitted, these results may be weighted in the risk assessment decision with negative in vivo results on the same endpoint, exposure data, or information from a structure activity relationship analysis These additional steps are required as genetic toxicity assays are used for hazard identification, requiring additional data to determine if the chemical is a carcinogen and/or what the quantitative risk associated with the positive result is or can be predicted to be. Weighing all of the available data in a safety assessment is an important part of the regulatory process as, in the case of genetic toxicity assays, the endpoints evaluated target varied genetic defects and, thus, may seem to show discordant results and no reproducibility.

This manuscript presents findings from a comprehensive assessment of the assumption that toxicity evaluation on the monomeric components of polymers provides a conservative approach in evaluating the potential toxicity of LMWOs and details issues and caveats regarding the use of monomer data for the assessment of LMWOs at dietary exposures $\leqslant$150 μg/p/d.

2. Methods

Both publicly-available data and data internal to OFAS were used for this assessment. A search of the publicly-available literature using combinations of terms related to the genetic toxicity and carcinogenicity of polymers, oligomers, and related monomers was conducted as a survey of data specific to food-contact polymers and oligomers. Relied on as an integral resource was Sheftel's *Indirect Food Additives and Polymers: Migration and Toxicology* (Sheftel, 2000), which is a compilation and review of the hazards of nearly 2000 polymeric materials used in food packaging. Also considered were data records in OFAS submitted by industry in support of food-additive petitions (FAPs) and FCNs which included full study reports, study summaries, and submitted literature articles, as well as OFAS' review of said studies. The types of toxicity tests used in the evaluation of genetic toxicity included reverse mutation (Ames) tests in bacteria, in vitro mammalian chromosomal aberration tests, in vitro mouse lymphoma

[1] http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm081818.htm accessed 8/30/10.

[2] http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/default.htm and http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm054658.htm both accessed 4/13/10.

$tk^{+/-}$ gene mutation assays, and in vivo mammalian erythrocyte micronucleus tests. When available, carcinogenicity bioassays in rodents were also considered. Representative structures of the materials were determined from publicly available sources (e.g., ChemIDPlus[3]) as well as from the information submitted in support of FAPs and FCNs and from internal FDA memoranda. Data that were fully reviewed by FDA were evaluated based on FDA's conclusions whereas data that were not reviewed by FDA (i.e., were reviewed by independent contracted reviewers or other entities) were considered based on the study author's conclusions. In the latter case, the conclusions are qualified as "reported".

3. Results

3.1. Toxicity data on polymers

Several studies that used intact polymeric materials as the test article were found in both the publicly-available databases and internal FDA files. In general, nearly all of the studies found in the public literature reported Negative results in the genetic toxicity tests with intact polymeric materials (Table 1). The tested polymers included linear polymers of acrylic acid with molecular weights between 2000 and 12,000 Daltons (Da), copolymers of acrylic and maleic acids, and cross-linked polyacrylate polymers. One genetic toxicity test reported as "positive" was a reverse mutation test in bacteria using *Salmonella typhimurium* strain TA 1538 without metabolic activation for the polymeric material methyloxirane polymerized with oxirane. The genetic toxicity and carcinogenicity studies listed in the book *Indirect Food Additives and Polymers: Migration and Toxicology* (included in Table 1) were also examined; however, these findings were less weighted in the analysis due to several factors including the lack of availability of the some studies in English translation, the antiquated nature of many of the studies (i.e., pre-Good Laboratory Practice), and/or the incomplete nature of the summary data.

All of the genetic toxicity tests in internal FDA files were either Negative, reported Negative, or Inconclusive (Table 2). Inconclusive findings were primarily the result of the limited usefulness of the data from toxicity tests on high-molecular weight test substances whose results would have to be considered with caution due to the expected limited absorption into cells in culture or in in vivo systems. Two carcinogenicity studies on two different polymers were found in OFAS' files. The first study in mice was Negative and tested poly(vinyl alcohol) with a molecular weight of 30,000–45000 Da (CASRN 9002–89-5) using an intravaginal exposure route. The second study in mice used dermal exposure to poly(*alpha*-olefins) and was determined to be Inconclusive due to high mortality as a result of infection of several test animals. Both studies are of limited use in determining oral carcinogenicity because of their routes of exposure.

3.2. Toxicity data on oligomers

As noted above, OFAS' safety evaluation considers that oligomeric materials with molecular weights at or below 1000 Da will migrate into the food matrix and be absorbed in the gut. As such, testing performed on this size fraction of the polymer would directly address the safety for the FCS. Although more useful, only a limited number of toxicity studies on oligomeric materials was found in both the publicly-available databases and internal FDA files.

Of the 11 oligomeric substances with toxicity data in internal FDA files, 17 genetic toxicity tests were performed and these were all Negative (Table 2). Information on the composition and molecular weight of the substances were, however, very limited in that several of the test substances were extracts and full characterization was not conducted by the submitter. In such cases comparative data with regard to migrating components and supporting data regarding the quantity used in testing was absent from the report. Genetic toxicity studies found in the public databases on the oligomers of halocarbon 3.1 oil (a mixture of chlorotrifluoroethylene oligomers of six and eight carbons) (Kutzman et al., 1990) and chlorotrifluoroethylene trimer acid (Godin et al., 1990) were all reported as Negative. Detailed chemical characterizations, including molecular weight information on the test substances, were not included in the study reports.

3.3. SAR on representative structures

A description of the use of computational toxicology (modeling) and SAR analysis to augment toxicity data submitted in support of the safety of new food-contact materials has been previously described (Bailey et al., 2005). SAR analyses are routinely performed in the review of food-contact materials, while more formal computational toxicology is performed on an as needed basis using a wide variety of toxicology modeling software (Arvidson et al., 2010). On the other hand, in the context of evaluating LMWOs, OFAS uses SAR analysis to evaluate the monomers and respective LMWO for the presence of structurally alerting features such as Ashby–Tennant structural alerts (Ashby and Tennant, 1991; Tennant and Ashby, 1991) or to identify structurally-related compounds with toxicological data. In the absence of data on the compound itself, a determination is made as to whether the monomer is structurally related to a compound with toxicological data or whether there are any alerting features in the monomer(s). If data are available on the monomer or identified using SAR, a determination is made as to the relevance of their findings to the LMWO, including whether the alerting features are present in the LMWOs. Additionally, the structure of the LMWOs is evaluated to determine if any new alerting features have been produced during the manufacture of the food-contact material and also to determine if there are any unique oligomeric materials, such as cyclic dimers and trimers present in conjunction with the typical linear oligomers expected from a polymerization. Any such findings might require additional data considerations.

3.4. Toxicity of monomers

Toxicity data on monomers used in the synthesis of food-contact polymers are much more abundant in the public literature as well as in FDA files, compared to reports on polymers or oligomers. As many of these monomers also migrate to food as a result of incomplete reactions, their safety at the expected exposure also must be addressed. As mentioned, at exposure levels above 1.5 μg/p/d in the diet, genetic toxicity tests are recommended. Some of these monomeric compounds are carcinogenic and, as they are impurities in the food additive and are not the food additive itself, are regulated based on the general safety standard (the Act, Section 409) using quantitative risk assessment procedures. The monomers reviewed from FDA files for this project are shown in Table 2.

4. Discussion

FDA is responsible for regulating food-contact materials, defined as substances intended for use as, or a component of, materials used in manufacturing, packing, packaging, transporting, or holding food if such use is not intended to have any technical effect in the food (Section 409(h)(6) of the Act). These substances are

[3] http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp accessed 4/13/10.

Table 1
Publicly-available genotoxicity and carcinogenicity studies on polymers, monomers, and oligomers.

Tested material	CASRN (if available, otherwise N/A)	Type of material – polymer; oligomer; monomer	Study type	Study Results	Ref. #
Allyl alcohol (AA)	107-18-6	Monomer	Non-standard published cancer bioassay	Inadequate	[37]
1,4-Benzenedicarboxylic acid, dimethyl ester (dimethyl terephthalate)	120-61-6	Monomer	2-yr NCI rat/mice bioassay	Equivocal	[50]
1,4-Butanediol	110-63-4	Monomer	2-yr NTP rat/mice bioassay	Negative	[54]
Caprolactam	105-60-2	Monomer	2-yr NTP rat/mice bioassay	Negative	[52]
Carboxymethyl cellulose	9004-32-4	Polymer	25 months feeding study in rats	Negative	[63]
Cellophane	9005-81-6; 9077-41-2	Polymer	Animal studies (s/c)	Positive	[60]
Cellulose	9004-34-6; 9006-02-4; 39394-43-9; 58968-67-5; 61991-21-7; 61991-22-8; 84503-75-3; 99331-82-5	Polymer	Lifetime feeding studies in rats and mice	Negative	[67]
Chlorotrifluoroethylene	79-38-9	Monomer	Ames test (*S. typhimurium*)	Negative	[66]
Chlorotrifluoroethylene	79-38-9	Monomer	In vivo SCE	Negative	[66]
Chlorotrifluoroethylene trimer acid	N/A	Oligomer	Ames test (*S. typhimurium* +S9)	Negative	[21]
Chlorotrifluoroethylene trimer acid	N/A	Oligomer	CHO/HGRT +S9	Negative	[21]
Chlorotrifluoroethylene trimer acid	N/A	Oligomer	Chromosomal aberrations and SCE in CHO cells +S9	Negative	[21]
Chlorotrifluoroethylene trimer acid	N/A	Oligomer	Morphological transformation in vitro in mouse BALB/c-3T3 cells +S9	Negative	[21]
Chlorotrifluoroethylene trimer acid	N/A	Oligomer	Unscheduled DNA synthesis in primary rat hepatocytes	Negative	[21]
Copolymer of acrylic and maleic acids	N/A	Polymer	Ames test (*S. typhimurium* +S9)	Negative	[92]
Copolymer of acrylic and maleic acids	N/A	Polymer	Mouse lymphoma assay	Negative	[92]
Copolymer of acrylic and maleic acids	N/A	Polymer	In vitro CHO cytogenetic assay	Negative	[92]
Copolymer of acrylic and maleic acids	N/A	Polymer	Unscheduled DNA synthesis in primary rat hepatocytes	Negative	[92]
Diethylene glycol	111-46-6	Monomer	2-yr rat bioassays	Equivocal	[17]
Ethylbenzene	100-41-4	Monomer	2-yr inhalation carcinogenicity study	Positive	[57]
Ethylene	74-85-1	Monomer	2-yr rat inhalation carcinogenicity study	Negative	[24]
Ethylene glycol	107-21-1	Monomer	2-yr rat/mice bioassays	Negative	[55]
Fluoroplastic-4	9002-84-0	Polymer	Animal studies (s/c)	Positive	[60]
Halocarbon 3.1 oil (a mixture of chlorotrifluoroethylene oligomers of six and eight carbons)	N/A	Oligomer	Ames test (*S. typhimurium* +S9)	Negative	[33]
Halocarbon 3.1 oil (a mixture of chlorotrifluoroethylene oligomers of six and eight carbons)	N/A	Oligomer	CHO/HGRT +S9	Negative	[33]
Halocarbon 3.1 oil (a mixture of chlorotrifluoroethylene oligomers of six and eight carbons)	N/A	Oligomer	Chromosomal aberrations and SCE in CHO cells +S9	Negative	[33]
Halocarbon 3.1 oil (a mixture of chlorotrifluoroethylene oligomers of six and eight carbons)	N/A	Oligomer	Morphological transformation in vitro in mouse BALB/c-3T3 cells +S9	Negative	[33]
Halocarbon 3.1 oil (a mixture of chlorotrifluoroethylene oligomers of six and eight carbons)	N/A	Oligomer	Unscheduled DNA synthesis in primary rat hepatocytes	Negative	[33]
Hexafluoroacetone	N/A	Monomer	Ames test (*S. typhimurium*)	Negative	[71]
Hexafluoropropylene	116-15-4	Monomer	Ames test (*S. typhimurium* with and without metabolic activation)	Negative	[70]
Hexamethylene diisocyanate	822-06-0	Monomer	2-yr inhalation carcinogenicity study	Negative	[46]
High-impact polystyrene upan-grade	N/A	Polymer	Feeding studies in rats	Positive	[28]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	DNA adduct formation, 32P-postlabeling (purified rat DNA)	Positive	[58]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	DNA adduct formation, 32P-postlabeling (CDI male rats)	Positive	[3]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	In vivo mammalian assays Dominant lethal assay (male S–D rats)	Negative	[3]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	Ames test with preincubation (*S. typhimurium* +S9)	Negative	[7]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	Gene mutation assay in yeast (*Saccharomyces cerevisiae* strain JDI)	Negative	[15]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	Sex-linked recessive lethal test (*Drosophila melanogaster*)	Negative	[15]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	Chromosome aberration test (CHO clone WBL −S9)	Positive	[18]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	Mouse micronucleus assay (ICR mice)	Negative	[19]

4,4′-Isopropylidenediphenol	80-05-7	Monomer	Ames test with preincubation (*S. typhimurium* +S9)	Negative	[23]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	Chromosome aberration test (CHO clone WBL +S9)	Negative	[25]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	Mammalian cell gene mutation assay, $tk^{+/-}$ locus (microwell method; L5178Y cells +S9 – two labs had inconsistent results)	Inconclusive	[26]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	Chromosome aberration test (CHO +S9)	Negative	[27]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	Sister chromatid exchange assay (CHO cells +S9)	Negative	[29]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	Ames test (*S. typhimurium* +S9)	Negative	[29]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	Syrian hamster embryo cell transformation assay (Syrian hamster embryo cells without activation)	Negative	[30]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	BALB/c-3T3 transformation assay (clone A31-1-13)	Negative	[36]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	Cell-free microtubule polymerization assay (microtubule proteins from bovine brain)	Positive	[42]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	Mammalian cell gene mutation assay, $tk^{+/-}$ locus (L5178Y cells +S9)	Negative	[45]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	2-yr oral study in mice	Negative	[48]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	2-yr oral study in rats	Inconclusive	[51]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	Microtubule assays for assessing aneuploidogenic potential (Chinese hamster V79 cells)	Positive	[51]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	Chromosomal aberrations in C57B1/6 mice (female oocytes and zygotes; male epididymal sperm) via various dosing regimens	Negative	[59]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	In vivo bone marrow micronucleus assay using male 102/ElxC3H/El)-F1 mice	Negative	[61]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	Cell-free microtubule polymerization assay (microtubule proteins from bovine brain)	Positive	[62]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	Micronucleus and microtubule assays for assessing aneuploidogenic potential (Chinese hamster V79 cells)	Positive	[64]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	Ames test (standard plate incorporation assay) (*S. typhimurium* +S9)	Negative	[64]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	Mammalian cell gene mutation assay, HPRT locus (CHO −S9)	Negative	[86]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	Alkaline elution/rat hepatocyte assay for DNA strand breaks (S–D rat hepatocytes)	Negative	[86]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	Ames test (*S. typhimurium* +S9)	Negative	[89]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	Mammalian cell gene mutation assay, Na+/K+ ATPase and hprt locus (Syrian hamster embryo cells without activation)	Negative	[91]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	Chromosome aberration test (Syrian hamster embryo cells without activation)	Negative	[93]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	Numerical aberrations assay, aneuploidy, polyploidy (Syrian hamster embryo cells without activation)	Inconclusive	[93]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	Syrian hamster embryo cell transformation assay (Syrian hamster embryo cells without activation)	Positive	[93]
4,4′-Isopropylidenediphenol	80-05-7	Monomer	DNA adduct formation, 32P-postlabeling (Syrian hamster embryo cells without activation)	Positive	[93]
Isoprene	78-79-5	Monomer	NTP carcinogenicity study	Positive	[93]
Linear polymer of acrylic acid (average MW 2000 g/mol) (Trade name Acrysol LMW-20X)	N/A	Polymer	Ames test (*S. typhimurium* +S9)	Negative	[92]
Linear polymer of acrylic acid (average MW 2000 g/mol) (Trade name Acrysol LMW-20X)	N/A	Polymer	Mouse lymphoma assay	Negative	[92]
Linear polymer of acrylic acid (average MW 2000 g/mol) (Trade name Acrysol LMW-20X)	N/A	Polymer	In vivo mouse bone marrow micronucleus assay	Negative	[92]
Linear polymer of acrylic acid (average MW 2000 g/mol) (Trade name Acrysol LMW-20X)	N/A	Polymer	Unscheduled DNA synthesis in primary rat hepatocytes	Negative	[92]
Linear polymer of acrylic acid (average MW 4500 g/mol) (Trade name Acrysol LMW-45N)	N/A	Polymer	Ames test (*S. typhimurium* +S9)	Negative	[92]
Linear polymer of acrylic acid (average MW 4500 g/mol) (Trade name Acrysol LMW-45N)	N/A	Polymer	Mouse lymphoma assay	Negative	[92]

(*continued on next page*)

Table 1 (*continued*)

Tested material	CASRN (if available, otherwise N/A)	Type of material – polymer; oligomer; monomer	Study type	Study Results	Ref. #
Linear polymer of acrylic acid (average MW 4500 g/mol) (Trade name Acrysol LMW-45N)	N/A	Polymer	In vitro CHO cytogenetic assay	Negative	[92]
Linear polymer of acrylic acid (average MW 4500 g/mol) (Trade name Acrysol LMW-45N)	N/A	Polymer	Unscheduled DNA synthesis in primary rat hepatocytes	Negative	[92]
Low density (high pressure) polyethylene (MW) 30,000–400,000	N/A	Polymer	Animal studies (s.c.)	Equivocal	[60]
Methyl acrylate	96-33-3	Monomer	2-yr inhalation carcinogenicity study in rats	Negative	[82]
Methylethyl cellulose	9004-59-5	Polymer	2-yr feeding studies in rats	Negative	[43]
Methyloxirane polymerized with oxirane	9038-95-3	Polymer	Ames test (*S. typhimurium* +S9)	Positive	[84]
N,*N*′-Methylenebisacrylamide cross-linked polyacrylate polymer	N/A	Polymer	Ames test (*S. typhimurium* +S9)	Negative	[92]
N,*N*′-Methylenebisacrylamide cross-linked polyacrylate polymer	N/A	Polymer	Mouse lymphoma assay	Negative	[92]
N,*N*′-Methylenebisacrylamide cross-linked polyacrylate polymer	N/A	Polymer	Unscheduled DNA synthesis in primary rat hepatocytes	Negative	[92]
N,*N*′-Methylenebisacrylamide cross-linked polyacrylate polymer	N/A	Polymer	In vivo rat bone marrow micronucleus assay	Negative	[92]
Norbornene fluoroalcohol	N/A	Intermediate	Ames test (*S. typhimurium* +S9)	Negative	[16]
N-Vinyl-2-pyrrolidinone	88-12-0	Monomer	12-month rat inhalation study	Positive	[32]
Octoxynol-1	9002-93-1/9004-87-9/9036-19-5/2315-67-5	Polymer	Ames test (*S. typhimurium* +S9; plate incorporation)	Negative	[65]
Octoxynol-40	9002-93-1/9036-19-5/9004-87-9	Polymer	2-yr carcinogenicity study in albino rats	Negative	[34]
Octoxynol-9 (Triton X-100)	9004-87-9/9036-19-5/9010-43-9/42173-90-0/9002-93-1	Polymer	Mammalian cell gene mutation assay, HPRT locus (T51B rat hepatocyte cells −S9)	Negative	[13]
Octoxynol-9 (Triton X-100)	9004-87-9/9036-19-5/9010-43-9/42173-90-0/9002-93-1	Polymer	Mammalian DNA repair/scheduled DNA synthesis assay using an adult rat hepatocyte cell line, T51B	Negative	[13]
Octoxynol-9 (Triton X-100)	9004-87-9/9036-19-5/9010-43-9/42173-90-0/9002-93-1	Polymer	Mammalian DNA alkaline unwinding assay using mouse lymphoma L5178Y/TK ± cells (−S9) with hydroxapatite chromatography	Negative	[20]
Octoxynol-9 (Triton X-100)	9004-87-9/9036-19-5/9010-43-9/42173-90-0/9002-93-1	Polymer	Chromosome aberration test (CHO +S9)	Inconclusive	[41]
Octoxynol-9 (Triton X-100)	9004-87-9/9036-19-5/9010-43-9/42173-90-0/9002-93-1	Polymer	Mammalian DNA alkaline unwinding assay using mouse lymphoma L5178Y/$tk^{+/-}$ cells (−S9) with hydroxyapatite chromatography	Negative	[97]
Octoxynol-9 (Triton X-100)	9004-87-9/9036-19-5/9010-43-9/42173-90-0/9002-93-1	Polymer	Mammalian cell gene mutation assay, $tk^{+/-}$ locus (L5178Y cells +S9?)	Negative	[99]
Octoxynol-9 (Triton X-100)	9004-87-9/9036-19-5/9010-43-9/42173-90-0/9002-93-1	Polymer	Ames test (*S. typhimurium* TA100 only, +S9; modified plate incorporation)	Negative	[102]
Perfluorobutylethylene	19430-93-4	Monomer	Ames test (*S. typhimurium* +S9)	Negative	[77]
Poloxamer 188	9003-11-6 (generic)	Polymer	2-yr carcinogenicity study in rats	Negative	[35]
Poloxamer 188	9003-11-6 (generic)	Polymer	2-yr carcinogenicity study in rats and dogs	Negative	[35]
Poloxamer 407	9003-11-6 (generic)	Polymer	Ames test (*S. typhimurium* +S9; plate incorporation)	Negative	[40]
Poly-1-butene (MW 50,000–100,000)	9003-29-6	Polymer	In vitro test with animal cells	Positive	[1]
Polyamides	N/A	Polymer	Animal cancer studies	Positive	[28]
Polycaprolactone	25248-42-4	Polymer extract	Ames test	Negative	[101]
Polycaprolactone	25248-42-4	Polymer extract	Ames test	Negative	[101]
Polydimethylsiloxane	9016-00-6; 63148-62-9	Polymer	1–2 yr study in rats (s/c of polyurethane and silicon)	Positive	[49]
Polyethylene glycol (PEG-4)	112-60-7/25322-68-3	Polymer	Ames test (*S. typhimurium* +S9; plate incorporation)	Negative	[47]
Polyethylene glycol (PEG-400)	25322-68-3	Polymer	Chromosomal aberrations (Chinese hamster epithelial liver cells – CHEL; +S9)	Negative	[5]
Polyethylene glycol (PEG-400)	25322-68-3	Polymer	Mammalian mutagenicity (CHO cells +S9)	Negative	[12]
Polyethylene glycol (PEG-400)	25322-68-3	Polymer	Sister chromatid exchange assay (CHO cells +S9)	Negative	[12]
Polyethylene glycol (PEG-400)	25322-68-3	Polymer	Unscheduled DNA synthesis (UDS) assay by radioactive thymidine incorporation using rat hepatocytes	Negative	[12]
Polyethylene glycol, monoalkyl esters	N/A	Polymer	6 month feeding study in rats	Negative	[100]

Polyethylene glycols (MW 500,000–10,000000)	25322-68-3	Polymer	Animal studies in mouse	Positive	[8]
Polyethylene terephthalate (MW 20,000–40,000)	29154-49-2	Polymer	73–82 weeks study in rodents	Negative	[6]
Polyethylene terephthalate (PET)	9003-68-3/25038-59-9	Extract (water)	Microtox genetic toxicity test (lyophilized cultures of a bioluminescent bacterium, V. fischeri NRRL-B-11177)	Negative	[14]
Polyethylene terephthalate (PET)	9003-68-3/25038-59-9	Extract (water)	Micronucleus tests using *Tradescantia* and *Allium cepa* (plants)	Negative	[14]
Polyethylene terephthalate (PET)	9003-68-3/25038-59-9	Extract (water)	Comet assay on human leukocytes	Negative	[14]
Polyhydroxybutyrate	N/A	Polymer	Ames test (*S. typhimurium* +S9; plate incorporation) and PCR of anti-apoptotic and proto-oncogenic genes	Negative	[2]
Polymer fabric consisting of polyethylene and polyethylene terephthalate	N/A	Polymer	Ames test (*S. typhimurium* +S9)	Negative	[44]
Polymethyl Methacrylate (MW <1,000,000	9011-14-7; 39404-54-1; 53663-63-1; 78206-73-2; 86438-94-0; 87210-32-0	Polymer	Animal studies	Positive	[60]
Polypropylene (MW 75,000–200,000)	9003-07-0	Polymer	Lifetime feeding studies in animals	Negative	[10]
Polyurethane	9009-54-5	Polymer	s/c study in rats	Positive	[49]
Polyvinyl acetate (MW 10,000–160,000)	9003-20-7; 76057-08-4	Polymer	Animal testing	Negative	[88]
Polyvinyl alcohol (MW 5,000–100,000)	9002-89-5	Polymer	Intravaginal administra-tion of 25% PVA solution in female mice.	Negative	[85]
Polyvinyl alcohol (PVA)	9002-89-5	Polymer	Ames test (*S. typhimurium* +S9; plate incorporation/preincubation)	Negative	[31]
Polyvinyl alcohol (PVA)	9002-89-5	Polymer	Mammalian DNA alkaline unwinding assay using mouse lymphoma L5178Y/ $tk^{+/-}$ cells (+S9)	Negative	[31]
Polyvinyl alcohol (PVA)	9002-89-5	Polymer	Mouse micronucleus test (m/f)	Negative	[31]
Polyvinyl chloride (MW 300,000–400,000)	9002-86-2; 8063-94-3; 51248-43-2; 93050-82-9	Polymer	30 week study in rats	Positive	[60]
Polyvinyl pyrrolidinone	9003-39-8	Polymer	Studies in rats	Positive	[4]
Propylene	115-07-1	Monomer	2-yr inhalation carcinogenicity study in rats	Negative	[53]
Rev7 (PIP-g-MA-MPEG polymer)	N/A	Polymer formulated in THF	Ames test (*S. typhimurium* +S9; with and without preincubation)	Negative	[90]
Rev7 (PIP-g-MA-MPEG polymer)	N/A	Polymer extracted in RPMI + 3% HS medium	Mammalian cell gene mutation assay, $tk^{+/-}$ locus (L5178Y cells +S9)	Positive	[90]
Rev7 (PIP-g-MA-MPEG polymer)	N/A	Polymer polar (saline) and non-polar (cottonseed oil) extracts	Mammalian erythrocyte micronucleus test (NMRI male and female mice)	Negative	[90]
Rubber and vulcanizates	N/A	Polymer	20 months study in mice	Positive	[87]
Rubber hydrochloride polymer	9006-00-2	Polymer	Studies in rodents	Positive	[60]
Siloxanes	N/A	Polymer	Case-control study	Negative	[11]
Sodium naphthalene sulfonate (SNS)	532-02-5	Monomer	Ames test (*S. typhimurium* +S9; plate incorporation)	Negative	[83]
Sodium polynaphthalene sulfonate (SPNS)	9084-06-4	Polymer	Ames test (*S. typhimurium* +S9; plate incorporation)	Negative	[38]
Styrene	100-42-5	Monomer	Occupational clinical study: chromosomal aberrations	Negative	[98]
Styrene	100-42-5	Monomer	(CAs) and binucleated cells (BNs) with micronuclei (MN) and on the level of single strand breaks (SSB) and SSB endonuclease III (Endo III) sites in peripheral lymphocytes	Positive	[98]
Styrene	100-42-5	Monomer	(CAs) and binucleated cells (BNs) with micronuclei (MN) and on the level of single strand breaks (SSB) and SSB endonuclease III (Endo III) sites in peripheral lymphocytes	Negative	[98]
Styrene polymer (polystyrene)(MW 50,000–200,000)	9003-53-6	Polymer	Studies in rodents	Positive	[60]
Terephthalic acid	100-21-0	Monomer	2-yr rat bioassays (2)	Positive	[22]
Tetraethylene glycol	112-60-7	Low molecular weight Polymer	Chromosomal aberrations (Chinese hamster epithelial liver cells – CHEL; +S9)	Positive	[5]
Tetrahydrofuran	109-99-9	Monomer	2-yr NTP rat/mice bioassay	Positive	[56]
Trialylamine cross-linked polyacrylate polymer	N/A	Polymer	Ames test (*S. typhimurium* +S9)	Negative	[92]
Trialylamine cross-linked polyacrylate polymer	N/A	Polymer	Mouse lymphoma assay	Negative	[92]
Trialylamine cross-linked polyacrylate polymer	N/A	Polymer	Unscheduled DNA synthesis in primary rat hepatocytes	Negative	[92]
Trialylamine cross-linked polyacrylate	N/A	Polymer	In vivo rat bone marrow micronucleus assay	Negative	[92]

(*continued on next page*)

Table 1 (*continued*)

Tested material	CASRN (if available, otherwise N/A)	Type of material – polymer; oligomer; monomer	Study type	Study Results	Ref. #
polymer					
Triethylene glycol	112-27-6	Trimer	2-yr carcinogenicity study in Osborne–Mendel rats	Negative	[17]
Triethylene glycol	112-27-6	Trimer	Mammalian mutagenicity (CHO cells +S9)	Negative	[94]
Triethylene glycol	112-27-6	Trimer	Mammalian in vivo clastogenic potential using the bone marrow aberration assay in male and female S-D rats	Negative	[95]
Triethylene glycol	112-27-6	Trimer	Ames test (*S. typhimurium* +S9; plate incorporation)	Negative	[96]
Triethylene glycol	112-27-6	Trimer	Sister chromatid exchange assay (CHO cells +S9)	Negative	[96]
Trifluoropropylene	677-21-4	Monomer	Ames test (*S. typhimurium* +S9)	Positive	[75]
Trimethylolpropane triacrylate cross-linked polyacrylate polymer	N/A	Polymer	Ames test (*S. typhimurium* +S9)	Negative	[92]
Trimethylolpropane triacrylate cross-linked polyacrylate polymer	N/A	Polymer	Mouse lymphoma assay	Negative	[92]
Trimethylolpropane triacrylate cross-linked polyacrylate polymer	N/A	Polymer	Unscheduled DNA synthesis in primary rat hepatocytes	Negative	[92]
Trimethylolpropane triacrylate cross-linked polyacrylate polymer	N/A	Polymer	In vivo rat bone marrow micronucleus assay	Negative	[92]
Vinyl acetate	N/A	Monomer	78-week drinking water study in mice	Positive	[39]
Vinyl chloride and vinyl acetate copolymer	34149-92-3	Polymer	Studies in mice	Positive	[9]
Vinyl chloride and vinyl chloride copolymer	68648-82-8	Polymer	Studies in rodents	Positive	[60]
Vinyl fluoride	75-02-5	Monomer	CHO cytogenetic (+S9)	Positive	[69]
Vinyl fluoride	75-02-5	Monomer	Ames test (*S. typhimurium* −S9)	Negative	[72]
Vinyl fluoride	75-02-5	Monomer	In vivo mouse micronucleus	Positive	[74]
Vinyl fluoride	75-02-5	Monomer	Ames test (*S. typhimurium* +S9)	Positive	[76]
Vinyl fluoride	75-02-5	Monomer	CHO/HGPRT (+S9)	Positive	[78]
Vinyl fluoride	75-02-5	Monomer	Unspecified (*E. coli*)	Equivocal	[80]
Vinylidene fluoride	75-38-7	Monomer	Ames test (*S. typhimurium*)	Equivocal	[68]
Vinylidene fluoride	75-38-7	Monomer	Ames test (*S. typhimurium*)	Negative	[68]
Vinylidene fluoride	75-38-7	Monomer	Ames test (*S. typhimurium*)	Positive	[73]
Vinylidene fluoride	75-38-7	Monomer	Unspecified (*E. coli*)	Positive	[79]
Vinylidene fluoride	75-38-7	Monomer	1-yr oral study in rats	Positive	[81]

This table only includes those publicly-available studies specifically considered by OFAS during food contact notification reviews. Please note that genetic toxicity and carcinogenicity are just two of the endpoints considered in the overall safety evaluation. Other endpoints are considered, as well, in the final evaluation (as deemed appropriate and/or based on availability of data).

Table 2
Polymeric materials safety data for genotoxicity from OFAS internal files.

Test material	CASRN	Material type	Genetic/Cancer Tox info	Result
1,3-Butanediol	107-88-0	Monomer	dominant lethal assay	Negative
1,3-Butanediol	107-88-0	Monomer	Chromosome aberration test using bone marrow cells	Negative
1,3-Benzenedimethanamine		Monomer	Ames tests (2)	Negative
1,3-Benzenedimethanamine		Monomer	In vitro chromosomal aberration test in Chinese Hamster Lung cells (CHL/IU)	Negative
1,3-benzenedimethanamine		Monomer	in vitro chromosomal aberration test in Chinese Hamster Ovary (CHO) cells	Negative
1,3-Benzenedimethanamine		Monomer	Mouse micronucleus test in bone marrow cells	Negative
1,3-Butanediol cyclic ester boric acid with 1-methyltrimethylene	2665-13-6	Monomer	Ames test	Negative
1,3-Butanediol cyclic ester boric acid with 1-methyltrimethylene	2665-13-6	Monomer	In vitro chromosome aberration test in CHL cells	Negative
1,3-Divinylimidazolidin-2-one	13811-50-2	Monomer	Ames test	Negative
1,3-Divinylimidazolidin-2-one	13811-50-2	Monomer	Chromosome aberration in V79 cells	Positive
1,3-Divinylimidazolidin-2-one	13811-50-2	Monomer	Hprt assay in CHO cells	Negative
1,3-Divinylimidazolidin-2-one	13811-50-2	Monomer	In vivo mouse micronucleus test	Negative
1,3-Divinylimidazolidin-2-one	13811-50-2	Monomer	Unscheduled DNA synthesis	Negative
1,3-Isobensofurandione, 4-chloro-, polymer with 1,3-benzenediamine,5-chloro-1,3-isobenzofurandione,1,3-isobenzofurandione, and 4,4′-(1-methylethylidene)bis[phenol]	536741-00-1	Polymer	Ames test	Inconclusive
1,3-Pentadiene	504-60-9	Monomer	Ames test	Negative
1,3-Pentadiene polymer with 2-methyl-2-butene	26813-14-9	Polymer	Ames test; *S. typhimurium*/*E. coli*	Negative
1,3-Pentadiene polymer with 2-methyl-2-butene	26813-14-9	Polymer	In vivo micronucleus test in bone marrow erythropoietic cells	Negative
1,4-Benzenediol, polymer with 1,1′-sulfonyl bis [4-chlorobenzene] and 4,4′-sulfonyl bis[phenol]	79293-56-4	Polymer	Ames test; *S. typhimurium*/microsome	Negative
1,4-Benzenediol, polymer with 1,1′-sulfonyl bis [4-chlorobenzene] and 4,4′-sulfonyl bis[phenol]	79293-56-4	Polymer	SCE – Sister Chromatid Exchange/CHO cells	Negative
1,4-Butanediol	110-63-4	Monomer	Ames tests (2)	Negative
1,4-Butanediol	110-63-4	Monomer	Chromosome aberration test Chinese Hamster Lung fibroblasts	Negative
1,4-Butanediol	110-63-4	Monomer	Hprt assay in CHO cells	Negative
1,4-Butanediol	110-63-4	Monomer	Drosophila SLRL Test	Negative
1,4-Butanediol	110-63-4	Monomer	chromosomal aberration study	Negative
1,6-Hexanediamine (hexamethylenediamine)	124-09-4	Monomer	Ames tests (10)	Negative
1,6-Hexanediamine (hexamethylenediamine)	124-09-4	Monomer	SCE – Sister Chromatid Exchange/CHO cells (2)	Negative
1,6-Hexanediamine (hexamethylenediamine)	124-09-4	Monomer	In vivo mouse micronucleus test	Negative
1,6-hexanediamine (hexamethylenediamine)	124-09-4	Monomer	Unscheduled DNA (2) synthesis assay (UDS) in rat hepatocytes	Negative
1,6-Hexanediamine (hexamethylenediamine)	124-09-4	Monomer	in vivo oral rat cytogenetic assay (2)	Negative
1-Butene, polymer with 1-propene, butene up to 35% by weight	29160-13-2	Polymer	Ames test; *S. typhimurium*, *E. coli*	Negative
1-Methylethenylbenzenepolymer with 2-methyl-2-butene and 1,3-penatadiene; 1,3-pentadiene polymer with 2-methyl-2-butene	62258-49-5	Polymer	In vivo micronucleus test in bone marrow erythropoietic cells	Negative
1-Vinylimidazole	1072-63-5	Monomer	Ames test	Negative
1-Vinylimidazole	1072-63-5	Monomer	Hprt assay	Negative
1-Vinylimidazole	1072-63-5	Monomer	In vitro chromosome aberration test	Negative
2,2,6,6-Tetramethyl-1-piperidinyloxy	2564-83-2	Monomer	Ames test; *S. typhimurium*	Negative
2,5-Furandione polymer with 2-methyl-1-propene, sodium salt	39612-00-5	Polymer	In vitro chromosomal aberration test in Chinese Hamster Ovary (CHO) cells	Negative
2,5-Furandione polymer with 2-methyl-1-propene, sodium salt	39612-00-5	Polymer	Ames test; *S. typhimurium*	Negative
2,5-Furandione polymer with 2-methyl-1-propene, sodium salt	39612-00-5	Polymer	CHO/HGPRT forward mutation assay	Negative
2-Hydroxyethyl methacrylate	868-77-9	Monomer	Ames test	Negative
2-Hydroxyethyl methacrylate	868-77-9	Monomer	Hprt assay	Negative
2-Hydroxyethyl methacrylate	868-77-9	Monomer	In vitro chromosome aberration test	Positive
2-Hydroxyethyl methacrylate	868-77-9	Monomer	In vitro micronucleus test	Positive

(*continued on next page*)

Table 2 (*continued*)

Test material	CASRN	Material type	Genetic/Cancer Tox info	Result
2-Hydroxyethyl methacrylate	868-77-9	Monomer	In vivo micronucleus test	Negative
2-Hydroxyethyl methacrylate	868-77-9	Monomer	Comet assay using human lymphocytes	Positive
2-Imidazolidinone, 1,3-diethenyl-copolymer with 1-ethenyl-1H-imidazole and 1-ethenyl-2-pyrrolidinone.	87865-40-5	Polymer	Ames test	Negative
2-*N*,*N*-Diethylaminoethyl methacrylate	105-16-8	Monomer	Ames test	Negative
2-*N*,*N*-Diethylaminoethyl methacrylate	105-16-8	Monomer	In vitro chromosome aberration test	Positive
2-*N*,*N*-Diethylaminoethyl methacrylate	105-16-8	Monomer	Mouse lymphoma assay	Positive
2-Propanone, polymer with formaldehyde	25619-09-4	Polymer	Ames test; *S. typhimurium*	Negative
2-Propen-1-ol, reaction products with 1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoro-6-iodohexane, dehydroiodinated, reaction products with epichlorohydrin and triethylenetetramine	464178-94-7	Polymer	In vivo micronucleus test	Negative
2-propen-1-ol, reaction products with 1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoro-6-iodohexane, dehydroiodinated, reaction products with epichlorohydrin and triethylenetetramine	464178-94-7	Polymer	In vitro chromosomal aberration test in human peripheral blood lymphocytes	Inconclusive
2-Propen-1-ol, reaction products with pentafluoroiodoethane-tetrafluoroethylene telomer, dehydroiodinated, reaction products with epichlorohydrin and triethylenetetramine	464178-90-3	Polymer	Ames test; *S. typhimurium*/*E. coli*	Negative
2-Propen-1-ol, reaction products with pentafluoroiodoethane-tetrafluoroethylene telomer, dehydroiodinated, reaction products with epichlorohydrin and triethylenetetramine	464178-90-3	Polymer	Mouse micronucleus test in bone marrow cells	Negative
2-Propen-1-ol, reaction products with pentafluoroiodoethane-tetrafluoroethylene telomer, dehydroiodinated, reaction products with epichlorohydrin and triethylenetetramine	464178-90-3	Polymer	In vitro chromosomal aberration test in human peripheral blood lymphocytes	Inconclusive
2-Propenoic acid, 2-methyl-, monoester with 1,2-propanediol, polymer with methyl 2-propenoate, 2-propenoic acid and sodium 2-propenoate	117675-55-5	Polymer	Ames test	Negative
2-propenoic acid, methyl ester, telomer with 1-dodecanethiol,C16–18 alkyl esters	174254-23-0	Oligomer	Ames test; *S. typhimurium*/*E. coli*	Negative
2-Propenoic acid, polymer with 2-ethyl-2[1-oxo-2-propenyl)oxy]methyl]-1,3-propanediyl di-2-propenoate and sodium 2-propenoate and glycerin (1,2,3-propanetiol, extractives of soluble oligomers obtained by extracting with distilled water)	76774-25-9/ 56-81-5	Polymer	Ames test; *S. typhimurium*/*E. coli*	Negative
2-Propenoic acid, polymer with *N*-ethenyl formamide, sodium salt, hydrolyzed, hydrochlorides	865596-61-8	Oligomer	Ames test; *S. typhimurium*/*E. coli*	Negative
2-Propenoic acid, polymer with *N*-ethenyl formamide, sodium salt, hydrolyzed, hydrochlorides	865596-61-8	Oligomer	Chromosome aberration in V79 cells	Negative
2-Propenoic acid, polymers with *N*,*N*-di-2-propenyl-2-propen-1-amine and hydrolyzed polyvinyl acetate, sodium salt, graft; or A grafted copolymer of cross-linked polyacrylic sodium salt polymer with polyvinyl alcohol (PVOH), superabsorbent polymer, SAP	166164-74-5	Polymer	Ames test	Negative
2-Propenoic acid, polymers with *N*,*N*-di-2-propenyl-2-propen-1-amine and hydrolyzed polyvinyl acetate, sodium salt, graft; or A grafted copolymer of cross-linked polyacrylic sodium salt polymer with polyvinyl alcohol (PVOH), superabsorbent polymer, SAP	166164-74-5	Polymer	Mouse lymphoma assay	Negative
2-Propenoic acid, polymers with *N*,*N*-di-2-propenyl-2-propen-1-amine and hydrolyzed polyvinyl acetate, sodium salt, graft; or A grafted copolymer of cross-linked polyacrylic sodium salt polymer with polyvinyl alcohol (PVOH), superabsorbent polymer, SAP	166164-74-5	Polymer	Unscheduled DNA synthesis	Negative
2-Propenoic acid, sodium salt, homopolymer	9003-04-7	Polymer	Ames test (3)	Negative
2-Propenoic acid, sodium salt, homopolymer	9003-04-7	Polymer	In vitro unscheduled DNA synthesis (UDS) in primary rat hepatocytes	Negative
2-Propenoic acid, sodium salt, homopolymer	9003-04-7	Polymer	Mouse micronucleus test in vitro	Negative
2-Propenoic acid, sodium salt, homopolymer	9003-04-7	Polymer	In vitro chromosomal aberration test in Chinese Hamster Lung cells (CHL)	Negative
2-Propenoic acid, sodium salt, homopolymer	9003-04-7	Polymer	Mouse lymphoma assay	Negative
2-Propenoic acid, sodium salt, homopolymer	9003-04-7	Polymer	Cytogenetic assay in Chinese Hamster Ovary (CHO) cells	Negative
2-Propenoic acid, sodium salt, homopolymer	9003-04-7	Polymer	Mouse bone marrow micronucleus assay	Negative
3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctylmethacrylate (C6FMA)	2144-53-8	Monomer	Ames test	Negative
3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctylmethacrylate (C6FMA)	2144-53-8	Monomer	In vitro chromosome aberration test	Negative
3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctylmethacrylate (C6FMA)	2144-53-8	Monomer	Mouse lymphoma assay	Equivocal
3-Chlorophthalic anhydride (3-ClPA)	117-21-5	Monomer	Ames test	Negative
3-Chlorophthalic anhydride (3-ClPA)	117-21-5	Monomer	In vitro chromosome aberration test	Negative

Table 2 (*continued*)

Test material	CASRN	Material type	Genetic/Cancer Tox info	Result
3-Chlorophthalic anhydride (3-ClPA)	117-21-5	Monomer	Mouse lymphoma assay	Negative
3-Chlorophthalic anhydride (3-ClPA)	117-21-5	Monomer	Micronucleus test in mice	Negative
3-Methyl-1,5-pentanediol	4457-71-0	Monomer	Ames test	Negative
3-Methyl-1,5-pentanediol	4457-71-1	Monomer	In vitro chromosomal aberration test in Chinese Hamster Lung cells (CHL)	Negative
3-Methyl-1,5-pentanediol	4457-71-2	Monomer	In vitro chromosomal aberration test in human peripheral blood lymphocytes	Negative
4-Chlorophthalic anhydride	118-45-6	Monomer	In vitro chromosome aberration test	Negative
4-Chlorophthalic anhydride	118-45-6	Monomer	Mouse lymphoma assay	Negative
4-Chlorophthalic anhydride	118-45-6	Monomer	Micronucleus test in mice	Negative
4-Methoxy-phenol	150-76-5	Monomer and impurity	Ames test	Negative
Acetic acid, hydroxy-, homopolymer	26124-68-5	Oligomer	Ames test	Negative
Acrylic acid methyl ester (methyl acrylate)	96-33-3	Monomer	Ames test	Negative
Acrylic acid methyl ester (methyl acrylate)	96-33-3	Monomer	In vitro chromosomal aberration test in Chinese hamster cells	Positive
Acrylic acid methyl ester (methyl acrylate)	96-33-3	Monomer	In vivo micronucleus test in bone marrow cells	Positive
Acrylic acid methyl ester (methyl acrylate)	96-33-3	Monomer	In vivo micronucleus test in bone marrow cells	Negative
Alcohols, C13–C15, branched and linear	85566-16-1	Monomer(s)	Ames tests (2)	Negative
Alcohols, C13–C15, branched and linear	85566-16-1	Monomer(s)	In vitro chromosome aberration tests (3)	Negative
Alcohols, C13–15, branched and linear	85566-16-1	Monomer(s)	Peroxisome proliferation in short-term oral repeat-dose	Negative
Alcohols, C13–C15, branched and linear, ethoxylated butoxylated	111905-53-4	Polymer (close to and contains ~1/3 LMWO)	Ames test	Negative
Alcohols, C13–C15, branched and linear, ethoxylated butoxylated	111905-53-4	Polymer (close to and contains ~1/3 LMWO)	In vivo mouse micronucleus test	Negative
Alkyl acrylate–alkyl methacrylate copolymer	470469-55-7	Surrogate for FCS of copolymer of lauryl methacrylate and behenyl methacrylate	Ames test	Negative
Alkyl acrylate–alkyl methacrylate copolymer	470469-55-7	Polymer	Ames test	Negative
Allyl alcohol (AA)	107-18-6	Monomer	Ames tests (3)	Positive
Allyl alcohol (AA)	107-18-6	Monomer	Chromosome aberration in V79 cells	Positive
Allyl alcohol (AA)	107-18-6	Monomer	Mouse L5178Y lymphoma assay	Positive
alpha-Methyl styrene	98-83-9	Monomer	Ames test	Negative
alpha-Methyl styrene	98-83-9	Monomer	CHO/HGPRT forward mutation assay	Negative
alpha-Methyl styrene	98-83-9	Monomer	in vitro chromosomal aberration test in Chinese Hamster Ovary (CHO) cells	Negative
Alumininum, hydroxybis[2,4,8,10-tetrakis(1,1-dimethylethyl)-6-hydroxy-12H-dibenzo[d,g]1,3,2]dioxaphosphocin 6-oxidato]-	151841-65-5	Polymer	Ames test	Negative
Alumininum, hydroxybis[2,4,8,10-tetrakis(1,1-dimethylethyl)-6-hydroxy-12H-dibenzo[d,g]1,3,2]dioxaphosphocin 6-oxidato]	151841-65-5	Polymer	Mouse lymphoma assay	Negative
Aminododecanoic acid	693-57-2	Monomer	Ames tests (2)	Negative
Aminododecanoic acid	693-57-2	Monomer	In vitro chromosomal aberration test in Chinese Hamster Ovary (CHO) cells (2)	Negative
Aminododecanoic acid	693-57-2	Monomer	CHO/HGPRT forward mutation assay	Negative
Aromatic petroleum hydrocarbon, hydrogenated or Resin A composed of: 14–32% styrene and substituted styrenes, 10–20% vinyl toluene, 2–8% indenes and substituted indenes and the remainder a wide variety of non-polymerizable hydrocarbons.	88526-47-0	Polymer	Ames test; S. typhimurium/ E. coli	Negative
Aromatic petroleum hydrocarbon, hydrogenated or Resin A composed of: 14–32% styrene and substituted styrenes, 10–20% vinyl toluene, 2–8% indenes and substituted indenes and the remaider a wide variety of non-polymerizable hydrocarbons	88526-47-0	Polymer	CHO cells cultured in vivo cytogenic assay with and without metabolic activation	Negative
Benzene, (1-methylethenyl-, polymer with 2-methyl-2-butene and 1,3-pentadiene	62258-49-5	Polymer	Ames test; *S. typhimurium*/ *E. coli*	Negative
Benzene, ethenyl-, polymer with 1,3 butadiene, hydrogenated, 4-methyl-1,3,2-dioxaborinan-2-yl 4-methyl-1,3,2-dioxaborolan-2-yl derivs	500224-31-7	Polymer	Ames tests (2)	Negative

(*continued on next page*)

Table 2 (*continued*)

Test material	CASRN	Material type	Genetic/Cancer Tox info	Result
Benzene, ethenyl-, polymer with 1,3 butadiene, hydrogenated, 4-methyl-1,3,2-dioxaborinan-2-yl 4-methyl-1,3,2-dioxaborolan-2-yl derivs	500224-31-7	Polymer	In vitro chromosomal aberration test in human peripheral blood lymphocytes	Negative
Benzene, ethenyl-, polymer with 2-methyl-1,3-butadiene, hydrogenated.	68648-89-5	Oligomer	Ames test; *S. typhimurium*/*E. coli*	Negative
Beta-(3,4-epoxycyclohexyl)-ethyltrimethoxysilane	3388-04-3	Monomer	Ames test	Negative
Beta-(3,4-epoxycyclohexyl)-ethyltrimethoxysilane	3388-04-3	Monomer	In vitro mouse lymphoma assay (MLA)	Negative
Bis(4-amino-3-methylcyclohexyl)methane	6864-37-5	Monomer	Ames test	Negative
Bis(4-amino-3-methylcyclohexyl)methane	6864-37-5	Monomer	In vitro chromosomal aberration test in Chinese Hamster Ovary (CHO) cells	Negative
Bis(4-amino-3-methylcyclohexyl)methane	6864-37-5	Monomer	In vitro Gene mutation assay in Chinese Hamster V79 cells	Negative
Bis-(4-aminocyclohexyl) methane	1761-71-3	Monomer	Ames tests (3)	Negative
Bis-(4-aminocyclohexyl) methane	1761-71-3	Monomer	In vivo cytogenetic study in NMRI mice by i.p. administration	Negative
C_{12}: lauryl methacrylate; C_{16}: hexyl methacrylate; C_{18}: octadecyl methacrylate		Surrogates for benzyl methacrylate	Ames test	Negative
C_{12}: lauryl methacrylate; C_{18}: octadecyl methacrylate		Surrogates for benzyl methacrylate	In vivo chromosomal aberration/micronucleus tests	Negative
Caprolactam	105-60-2	Monomer	Mouse lymphoma assay (MLA) $tk^{+/-}$ cells	Negative
Caprolactam	105-60-2	Monomer	In vitro chromosomal aberration test in Chinese Hamster Ovary (CHO) cells	Negative
Caprolactam	105-60-2	Monomer	In vitro HGPRT assay in V79 cells	Negative
Caprolactam	105-60-2	Monomer	In vitro chromosomal aberration test in Chinese Hamster Ovary (CHO) cells	Negative
Caprolactam	105-60-2	Monomer	Unscheduled DNA synthesis assay (UDS) in rat hepatocytes	Negative
Caprolactam	105-60-2	Monomer	in vitro human lymphocyte assays	Inconclusive
Caprolactam	105-60-2	Monomer	Ames tests (23)	Negative
Caprolactam	105-60-2	Monomer	In vivo mouse bone marrow micronucleus assay	Negative
Carbon monoxide–olefin polymers	111190-67-1; 88995-51-1	Polymer	Ames test	Negative
Carbon monoxide–olefin polymers	111190-67-1; 88995-51-1	Polymer	Mouse L5178Y lymphoma assay	Inconclusive
Copolymer of poly(fluorooctyl methacrylate), 2-*N*,*N*-diethylaminoethylmethacrylate, 2-hydroxyethylmethacrylate, and 2,2′-ethylenedioxydiethyldimethacrylate	863408-19-9	Polymer	Ames test	Negative
Copolymer of poly(fluorooctyl methacrylate), 2-*N*,*N*-diethylaminoethylmethacrylate, 2-hydroxyethylmethacrylate, and 2,2′-ethylenedioxydiethyldimethacrylate	863408-19-9	Polymer	In vitro chromosomal aberration test in Chinese hamster cells	Negative
Cross-linked reaction product of an acrylic resin, a silane coupling agent, and an urethane prepolymer		Polymer	Ames test	Negative
Diethylene glycol	111-46-6	Monomer	Ames tests (3)	Negative
Diethylene glycol	111-46-6	Monomer	Chromosome aberration test Chinese Hamster Lung fibroblasts	Negative
Diethylene glycol	111-46-6	Monomer	Hgprt assay in CHO cells	Negative
Diethylene glycol	111-46-6	Monomer	Dominant lethal assay	Negative
Diethylene glycol	111-46-6	Monomer	Micronucleus assay	Negative
Dipentene/butadiene/styrene resins			Ames test	Negative
Dodecanedioic acid	693-23-2	Monomer	Ames test	Negative
Dodecanedioic acid	693-23-2	Monomer	In vivo mouse (Crl:CD-1(ICR)BR) bone marrow micronucleus assay	Negative
Dodecylmercaptan	112-55-0	Chain transfer agent	Ames test	Negative
Dodecylmercaptan	112-55-0	Chain transfer agent	Mouse lymphoma assay	Negative
Ethylbenzene	100-41-4	Monomer	Ames test; *S. typhimurium*, *E. coli*	Negative
Ethylbenzene	100-41-4	Monomer	Mouse lymphoma assay	Positive
Ethylbenzene	100-41-4	Monomer	Sister chromatid exchange assay	Positive
Ethylbenzene	100-41-4	Monomer	mouse peripheral blood micronucleus test	Positive
Ethylene	74-85-1	Monomer	Ames tests (5+)	Negative

Table 2 (*continued*)

Test material	CASRN	Material type	Genetic/Cancer Tox info	Result
Ethylene	74-85-1	Monomer	In vivo mouse and rat micronucleus tests	Negative
Ethylene	74-85-1	Monomer	Bone marrow micronucleus tests in mice and rats	Negative
Ethylene	74-85-1	Monomer	In vitro chromosomal aberration test in Chinese Hamster Ovary (CHO) cells	Negative
Ethylene glycol	107-21-1	Monomer	Ames test	Negative
Ethylene glycol	107-21-1	Monomer	In vitro chromosomal aberration test in Chinese Hamster Ovary (CHO) cells	Negative
Ethylene glycol	107-21-1	Monomer	Mouse L5178Y lymphoma assay	Negative
Ethylene, tetrafluoro-, polymer with 1,1-difluoroethylene and hexafluoropropene; ethanol extracts	25190-89-0	Oligomer	Ames test; *S. typhimurium*/ *E. coli*	Negative
Film extract of a cross-linked reaction product of an acrylic resin, a silane coupling agent, and an urethane prepolymer		Oligomer	Ames test; *S. typhimurium*/ *E. coli*	Negative
Formamide	75-12-7	Monomer	Ames test	Negative
Formamide	75-12-7	Monomer	Micronucleus assay	Negative
Formamide	75-12-7	Monomer	Drosophila sex-linked recessive assay	Negative
Hexafluoropropylene	116-15-4	Monomer	Ames test	Negative
Hexafluoropropylene	116-15-4	Monomer	Hgprt assay in CHO cells	Negative
Hexafluoropropylene	116-15-4	Monomer	Dominant lethal assay	Negative
Hexafluoropropylene	116-15-4	Monomer	In vivo micronucleus test	Positive
Hexafluoropropylene	116-15-4	Monomer	In vitro chromosomal aberration test in Chinese Hamster Ovary (CHO) cells	Positive
Hexamethylene diisocyanate	822-06-0	Monomer	Ames tests (2)	Negative
Hexamethylene diisocyanate	822-06-0	Monomer	Hgprt assay in CHO cells	Negative
Hexamethylene diisocyanate	822-06-0	Monomer	In vivo mouse micronucleus test	Negative
Hexanedioic acid, polymer with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol,α-hydroxy-ω-hydroxypoly(oxy-1,4-butanediyl),3-methyl-1,5-pentanediol and 1-methyl-1,3-propanediyl bis[(6-isocyanatohexyl)carbamate]	622366-97-6	Oligomer	Ames test; *S. typhimurium*/ *E. coli*	Negative
Hexanedioic acid, polymer with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol,α-hydroxy-ω-hydroxypoly(oxy-1,4-butanediyl),3-methyl-1,5-pentanediol and 1-methyl-1,3-propanediyl bis[(6-isocyanatohexyl)carbamate]	622366-97-6	Oligomer	In vitro chromosomal aberration test in Chinese Hamster Ovary (CHO) cells	Negative
Hydrogenated polymers prepared from one or more of the following: 1-octene (0–100 wt.%), 1-decene (0–100 wt.%), and 1-dodecene (0–100 wt.%).		Polymer	Ames test	Negative
Hydrogenated polymers prepared from one or more of the following: 1-octene (0–100 wt.%), 1-decene (0–100 wt.%), and 1-dodecene (0–100 wt.%).		Polymer	In vitro chromosomal aberration test in Chinese Hamster Ovary (CHO) cells	Negative
Hydrogenated polymers prepared from one or more of the following: 1-octene (0–100 wt.%), 1-decene (0–100 wt.%), and 1-dodecene (0–100 wt.%).		Polymer	In vitro chromosomal aberration test in human peripheral blood lymphocytes	Negative
Hydrogenated polymers prepared from one or more of the following: 1-octene (0–100 wt.%), 1-decene (0–100 wt.%), and 1-dodecene (0–100 wt.%).		Polymer	Ames test	Negative
Hydrogenated polymers prepared from one or more of the following: 1-octene (0–100 wt.%), 1-decene (0–100 wt.%), and 1-dodecene (0–100 wt.%).		Polymer	In vitro mouse micronucleous assay	Negative
Hydrogenated polymers prepared from one or more of the following: 1-octene (0–100 wt.%), 1-decene (0–100 wt.%), and 1-dodecene (0–100 wt.%)		Polymer	Ames test	Inconclusive
Isophorone diisocyanate	4098-71-9	Monomer	Ames test	Negative
Isophthalic acid	121-91-5	Monomer	Ames tests (4)	Equivocal
Isophthalic acid	121-91-5	Monomer	In vitro chromosomal aberration test in Chinese Hamster Ovary (CHO) cells	Negative
Isophthalic acid	121-91-5	Monomer	Hgprt assay in CHO cells	Negative
Isophthalic acid	121-91-5	Monomer	Mouse L5178Y lymphoma assay	Negative
Laurolactam	947-04-6	Monomer	Ames tests (2)	Negative
Laurolactam	947-04-6	Monomer	In vitro chromosomal aberration test in human peripheral blood lymphocytes	Negative
Laurolactam	947-04-6	Monomer	Hprt assay in CHO cells	Negative
Laurolactam	947-04-6	Monomer	Unscheduled DNA synthesis assay (UDS) in rat hepatocytes	Negative
Laurolactam	947-04-6	Monomer	In vivo oral rat cytogenetic assay	Negative

(*continued on next page*)

Table 2 (*continued*)

Test material	CASRN	Material type	Genetic/Cancer Tox info	Result
Lauryl methacrylate	142-90-5	Monomer	Ames test (2)	Negative
Lauryl methacrylate	142-90-5	Monomer	In vitro chromosomal aberration test	Negative
Lauryl methacrylate	142-90-5	Monomer	In vivo mouse micronucleus test	Negative
LMWO of 1,3-butadiene, 2-methyl, homopolymer, of cis-1,4-configuration, cyclized		Synthesized oligomer, unoxidized	Ames test	Negative
LMWO of 1,3-butadiene, 2-methyl, homopolymer, of cis-1,4-configuration, cyclized		Synthesized oligomer, unoxidized	In vivo mouse micronucleus test	Negative
LMWO of 1,3-butadiene, 2-methyl, homopolymer, of cis-1,4-configuration, cyclized		Synthesized oligomer, oxidized	Ames test	Negative
LMWO of 1,3-butadiene, 2-methyl, homopolymer, of cis-1,4-configuration, cyclized		Synthesized oligomer, oxidized	In vivo mouse micronucleus test	Negative
LMWO of poly(alkyl acrylate) syn.		Synthesized oligomer	Ames test	Negative
LMWO of poly(alkyl acrylate) syn.		Synthesized oligomer	In vitro chromosomal aberration test in Chinese Hamster Lung cells (CHL)	Negative
LMWO of poly(alkyl methacrylate) syn.		Synthesized oligomer	Ames test	Negative
Maleic anhydride polymer with ethyl acrylate and vinyl acetate hydrolyzed or 2,5-furandione, polymer with ethyl 2-propenate, ethenyl acetate, and xylene		Polymer	Ames test; *S. typhimurium*/microsome	Negative
Maleic anhydride polymer with ethyl acrylate and vinyl acetate hydrolyzed or 2,5-furandione, polymer with ethyl 2-propenate, ethenyl acetate, and xylene		Polymer	In vitro *Saccharomyces cerevisiae* D7/mammalian-microsome mutagenicity test	Negative
Maleic anhydride polymer with ethyl acrylate and vinyl acetate hydrolyzed or 2,5-furandione, polymer with ethyl 2-propenate, ethenyl acetate, and xylene		Polymer	Sister chromatid exchange studies on somatic cells of Chinese hamster	Negative
Maleic anhydride polymer with ethyl acrylate and vinyl acetate hydrolyzed or 2,5-furandione, polymer with ethyl 2-propenate, ethenyl acetate, and xylene		Polymer	Nucleus anomaly test in somatic interphase of chinese hamster	Negative
Maleic anhydride polymer with ethyl acrylate and vinyl acetate hydrolyzed or 2,5-furandione, polymer with ethyl 2-propenate, ethenyl acetate, and xylene		Polymer	Autoradiographic DNA repair test on rat hepatocytes	Negative
Maleic anhydride polymer with ethyl acrylate and vinyl acetate hydrolyzed or 2,5-furandione, polymer with ethyl 2-propenate, ethenyl acetate, and xylene		Polymer	Autoradiographic DNA repair test on human fibroblasts	Negative
Methacrylic acid	79-41-4	Monomer	Ames test	Negative
Methyl acrylate	96-33-3	Monomer	Ames test	Negative
Methyl acrylate	96-33-3	Monomer	In vitro chromosomal aberration test in Chinese Hamster Lung cells (CHL)	Positive
Methyl acrylate	96-33-3	Monomer	In vivo micronucleus test	Equivocal
Methyl acrylate	96-33-3	Monomer	Mouse lymphoma assay	Positive
Methyl methacrylate	80-62-6	Monomer	Ames test	Negative
Methyl methacrylate	80-62-6	Monomer	Mouse lymphoma assay	Positive
Methyl methacrylate	80-62-6	Monomer	Hprt assay	Positive
Methyl methacrylate and trimethylolpropane trimethacrylate copolymer		Polymer	Ames test; *S. typhimurium*/*E. coli*	Negative
Mixture of alkyl methacrylates		Surrogates for benzyl methacrylate	Ames test	Negative
Mixture of alkyl methacrylates		Surrogates for benzyl methacrylate	In vitro chromosomal aberration test	Negative
Mixture of branched and normal C12–C18 AMAs (not C17)		Monomer mix	Ames test	Negative
Mixture of branched and normal C12–C18 AMAs (not C17)		Monomer mix	In vitro gene mutation assay in Chinese Hamster V79 cells	Negative
Modified polydimethylsiloxane	Mixture	Monomer	Ames tests (3) on hexamethyldisiloxane	Negative
Modified polydimethylsiloxane	Mixture	Monomer	Sister chromatid exchange assay on hexamethyldisiloxane	Negative
Modified polydimethylsiloxane	Mixture	Monomer	Mouse lymphoma assay on hexamethyldisiloxane	Negative
Modified polydimethylsiloxane	Mixture	Monomer	Alkaline elution assay on hexamethyldisiloxane	Negative
Modified polydimethylsiloxane	Mixture	Monomer	In vivo chromosomal aberration/micronucleus tests on hexamethyldisiloxane	Negative
Modified polydimethylsiloxane	Mixture	Monomer	In vitro chromosomal aberration test	Inconclusive
m-Phenylenediamine (*m*-PD)	108-45-2	Monomer	Ames test	Equivocal
m-Phenylenediamine (*m*-PD)	108-45-2	Monomer	SCE cell transformation assay	Positive
m-Phenylenediamine (m-PD)	108-45-2	Monomer	Chromosomal aberration assay in *Allium cepa*	Positive
m-Phenylenediamine (m-PD)	108-45-2	Monomer	Rodent hepatocyte UDS assay	Negative
m-Xylylene diisocyanate	3634-83-1	Monomer	Ames test	Negative

Table 2 (*continued*)

Test material	CASRN	Material type	Genetic/Cancer Tox info	Result
m-Xylylene diisocyanate	3634-83-1	Monomer	In vitro chromosomal aberration test	Positive
Naphtha (petroleum). Light steam-cracked arom., polymer with light steamed arom. petroleum naphtha piperylene conc. and medium steam cracked arom.	68527-25-3	Polymer	Ames tests (4)	Negative
Naphtha (petroleum). Light steam-cracked arom., polymer with light steamed arom. Petroleum naphtha piperylene conc. and medium steam cracked arom.	68527-25-3	Polymer	In vivo mammalian bone marrow micronucleus assay	Negative
N-Vinylformamide	13162-05-5	Monomer	Ames test	Negative
N-Vinylformamide	13162-05-5	Monomer	Hgprt assay in CHO cells	Negative
N-Vinylformamide	13162-05-5	Monomer	In vivo mouse micronucleus test	Negative
Octadecyl (C18) methacrylate	32360-05-7	Monomer	Ames test	Negative
Octadecyl (C18) methacrylate	32360-05-7	Monomer	In vivo mouse micronucleus test	Negative
Perfluoroethylhexyl acrylate (13FA)	17527-29-6	Monomer	Ames test	Negative
Perfluoroethylhexyl acrylate (13FA)	17527-29-6	Monomer	In vitro chromosomal aberration test in Chinese Hamster Lung cells (CHL)	Negative
Perfluoroethylhexyl acrylate (13FA)	17527-29-6	Monomer	In vivo mouse bone marrow micronucleus assay	Negative
Perfluorohexanoic acid (PFHA)	307-24-4		Ames test	Negative
Perfluoropolyether diol	88645-29-8	Monomer	Ames test	Negative
Perfluoropolyether diol	88645-29-8	Monomer	In vitro chromosomal aberration test in Chinese Hamster Ovary (CHO) cells	Negative
Phenol, 4-(1,1-dimethylethyl)-, polymer with sulfur chloride	60303-68-6	Polymer	Ames test; *S. typhimurium*	Negative
Phenol, 4-(1,1-dimethylethyl)-, polymer with sulfur chloride	60303-68-6	Polymer	In vitro chromosomal aberration test	Negative
Phthalic anhydride (PA)	85-44-9	Monomer	Ames test	Negative
Phthalic anhydride (PA)	85-44-9	Monomer	In vitro chromosome aberration test	Negative
Phthalic anhydride (PA)	85-44-9	Monomer	Mouse lymphoma assay	Positive
Piperylene	504-60-9	Monomer	Ames test; *S. typhimurium*	Negative
Poly(alkyl (C16–C22) acrylate)	27029-57-8	Polymers	Ames test	Negative
Poly(alkyl (C16-C22) acrylate)	27029-57-8	Polymers	Rat liver chromosomal aberration assay	Negative
Polyalkyl (C16-C22) acrylate		Polymer	Bacterial mutation study *Saccharomyces* gene conversion assay	Negative
Polyalkyl (C16-C22) acrylate		Polymer	Rat liver chromosomal aberration assay	Negative
Polyalkyl (C16-C22) acrylate		Polymer	BHK transformation assay	Negative
Polyalkyl (C16-C22) acrylate		Polymer	integrity of rat liver DNA in vivo	Negative
Polybetaine polysiloxane copolymer	102523-96-6/ 146905-77-3	Polymer	Ames test; *S. typhimurium*	Negative
Polybetaine polysiloxane copolymer	102523-96-6/ 146905-77-3	Polymer	In vitro chromosomal aberration test in Chinese Hamster Ovary (CHO) cells	Negative
Polybetaine polysiloxane copolymer	146905-77-3	Polymer	Ames test	Negative
Polybetaine polysiloxane copolymer	146905-77-3	Polymer	In vitro chromosomal aberration test	Negative
Polyethylene glycol monoacrylate	26403-58-7	Monomer	Ames test	Positive
Propanoic acid, 3-hydroxy-2-(hydroxymethyl)-2-methyl-, polymers with 5-isocyanato-1-(isocyanatomethyl)-1,3,3-trimethylcyclohexane and reduced Me esters of reduced polymerized oxidized tetrafluoroethylene, compounds with triethylamine	328389-91-9	Oligomer	Ames test; *S. typhimurium*/ *E. coli*	Negative
Sebacic acid (decanedioic acid)	111-20-6	Monomer	Ames tests (3)	Negative
Sebacic acid (decanedioic acid)	111-20-6	Monomer	In vivo mouse micronucleus test	Negative
Siloxanes and silicones	68440-71-1	Monomer	Ames test	Negative
Siloxanes and silicones	68440-71-1	Monomer	In vitro chromosomal aberration test in Chinese Hamster Ovary (CHO) cells	Negative
Siloxanes and silicones	68440-71-1	Monomer	Cell transformation assay	Negative
Siloxanes and silicones	68440-71-1	Monomer	Hgprt assay in CHO cells	Negative
Siloxanes and silicones	68440-71-1	Monomer	In vivo micronucleus test	Negative
Siloxanes and silicones, di-Me, hydrogen-terminated, reaction products with acrylic acid and 2-ethyl-2[(2-propenyloxy)methyl]-1,3-propanediol	155419-56-0	Polymer	Ames test; *S. typhimurium*	Negative
Siloxanes and silicones, dimethyl, polymers with silica-1,1,1-trimethyl-*N*-(trimethylsilyl)silanamine hydrolysis product and silicic acid trimethylsilyl ester	159002-21-8	Polymer	Ames test; *S. typhimurium*/ *E. coli*	Negative

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Table 2 (*continued*)

Test material	CASRN	Material type	Genetic/Cancer Tox info	Result
Sodium acrylate/styrene sulfonate copolymer; 2-propenoic acid, polymer with sodium 4-ethylene benzene sulfonate, sodium salt, disodium disulfite, and peroxy-disulfuric acid, diammonium salt initiated		Oligomer	Ames test; *S. typhimurium*/ *E. coli*	Negative
Styrene 4–32% or substituted styrenes			Ames test	Negative
Sulfolane or tetrahydrothiopene-1,1-dioxide	126-33-0	Monomer	Ames test	Negative
Sulfolane or tetrahydrothiopene-1,1-dioxide	126-33-0	Monomer	Sister chromatid exchange assay	Negative
Sulfolane or tetrahydrothiopene-1,1-dioxide	126-33-0	Monomer	In vitro mouse lymphoma assay (MLA)	Positive
Synthetic Wax polymer		Polymer	Ames test; *S. typhimurium*	Negative
Terephthalic acid	100-21-0	Monomer	Ames tests (4)	Negative
Terephthalic acid	100-21-0	Monomer	In vitro chromosomal aberration test in Chinese Hamster Lung cells (CHL)	Negative
Terephthalic acid	100-21-0	Monomer	In vitro chromosomal aberration test in human peripheral blood lymphocytes	Negative
Terephthalic acid	100-21-0	Monomer	Single strand break analysis: primary rat hepatocytes	Negative
Terephthalic acid	100-21-0	Monomer	In vitro micronucleus test: human peripheral blood lymphocytes	Negative
Terephthalic acid	100-21-0	Monomer	In vivo mouse micronucleus test	Negative
tert-Butyl methacrylate	585-07-9	Monomer	Ames test	Negative
Tetrahydrofuran	100-99-9	Monomer	Ames tests (2)	Negative
Tetrahydrofuran	109-99-9	Monomer	In vitro chromosomal aberration test in Chinese Hamster Ovary (CHO) cells	Negative
Tetrahydrofuran	109-99-9	Monomer	SCE – Sister Chromatid Exchange/CHO cells	Negative
Tetrahydrofuran	109-99-9	Monomer	Mouse peripheral blood micronucleus test	Equivocal
Tetrahydrofuran	109-99-9	Monomer	*Drosophila* SLRL test	Negative
Tetrahydrofuran	109-99-9	Monomer	In vivo mouse bone marrow chromosomal aberration assay	Negative
Tricyclodecanedimethanol	26160-83-8	Monomer	In vitro chromosomal aberration test	Negative
Tricyclodecanedimethanol	26160-83-8	Monomer	Ames test	Negative
Tricyclodecanedimethanol	26160-83-8	Monomer	Hprt assay	Negative
Triethylene glycol dimethacrylate	109-16-0	Monomer	Ames test	Equivocal
Triethylene glycol dimethacrylate	109-16-0	Monomer	Hprt assay	Positive
Triethylene glycol dimethacrylate	109-16-0	Monomer	Comet assay	Positive
Triethylene glycol dimethacrylate	109-16-0	Monomer	In vitro chromosomal aberration test	Positive
Triethylenetetramine	112-24-3	Monomer	CHO/HGPRT forward mutation assay	Equivocal
Triethylenetetramine	112-24-3	Monomer	In vivo mouse micronucleus assay	Negative
Triethylenetetramine	112-24-3	Monomer	SCE – Sister Chromatid Exchange/CHO cells	Positive
Triethylenetetramine	112-24-3	Monomer	Ames tests (3)	Positive
Triethylenetetramine	112-24-3	Monomer	Clastogenic activity micronucleus study with SW mice	Negative
Triethylenetetramine	112-24-3	Monomer	Chinese Hamster Ovary (CHO) gene mutation assay	Equivocal
Triethylenetetramine	112-24-3	Monomer	Unscheduled DNA synthesis	Positive
Trimethylolpropane	77-99-6	Monomer	Ames test	Negative
Trimethylolpropane	77-99-6	Monomer	In vitro chromosomal aberration test	Negative
Vinyl alcohol, polymers (polyvinyl alcohol)	9002-89-5	Polymer	Ames test	Negative
Vinyl alcohol, polymers (polyvinyl alcohol)	9002-89-5	Polymer	In vitro gene mutation assay in Chinese Hamster V79 cells	Negative
Vinyl alcohol, polymers (Polyvinyl alcohol)	9002-89-5	Polymer	*Saccharomyces cerevisiae* mutagenicity test	Negative
γ-Isocyanato-propyltrimethoxysilane	15396-00-6	Monomer	Ames test	Negative
γ-Isocyanato-propyltrimethoxysilane	15396-00-6	Monomer	In vitro chromosomal aberration test	Negative

This table only includes those internally-available studies specifically considered by OFAS during food contact notification reviews. Please note that genetic toxicity and carcinogenicity are just two of the endpoints considered in the overall safety evaluation. Other endpoints are considered, as well, in the final evaluation.

usually industrial compounds by their nature and they are not intended to be components of food, but migrate due to their use in transporting, storing, and packaging of food. The former translates to the fact that they are usually not without toxicity and they may have overlapping regulatory submissions resulting in publicly-available data. The later relates to the fact that their exposure evaluation often is complex in that it considers the migration of small (typically $\leqslant$1000 Da) molecules from the product into the food in determining estimated daily intakes. FDA is rather unique in its approach to evaluating polymers in that it evaluates the monomeric materials that migrate to food and also the potential impurities from the incomplete reactions, i.e., the low-molecular weight oligomers.

The FDA's current approach to the safety evaluation of FCSs is based on a tiered toxicity testing strategy for all materials for which migration to food is expected. This includes the evaluation of the safety of LMWO that are expected to migrate to food from the FCS. Although sometimes conducted, toxicity testing on polymers has limited usefulness in that these often large molecules are not the primary migrant to food, they are not expected to cross cellular membranes or outer cell walls in in vitro systems, and they have limited absorption in the gastrointestinal tract of animals. Accordingly, any testing would have limited interpretability with regard to the absorbable factors' ability to elicit any potential toxic effects. Industry submitters may have studies conducted on the polymer or the monomers, as these studies are not limited by generation of testing material, whereas in order to generate sufficient testing material on the LMWO, the reaction parameters would either have to be altered, the polymer would have to be size fractioned, or a separate 'facsimile' would have to be synthesized. All of these are costly approaches and are often argued as unnecessary given the weight of evidence regarding data on the monomers, what is known about the reaction of monomers during polymerization, and SAR. This continual debate has led to several resolutions, such as toxicity testing of representative facsimiles, extracts, representative dimers or trimers, and acceptance of monomer data up to 150 μg/p/d for the endpoints of genetic toxicity as an indicator of the potential carcinogenicity of the substance.

This study was conducted to evaluate the often-submitted approach in determining the safety of oligomeric materials with dietary exposures $\leqslant$150 μg/p/d based on the safety data for the monomers. At exposures above 1.5 but at or below 150 μg/p/d, OFAS recommends that two in vitro genetic toxicity assays be conducted to determine the genetic toxicity of the substance as an indicator of the potential carcinogenicity. OFAS' recommendation for genetic toxicity data became guidance when the Food and Drug Administration Modernization Act of 1997 created the food-contact notification (FCN) program. At that time, notifiers began to argue for the use of primarily genetic toxicity and carcinogenicity data on the monomers in making safety decisions. The position was based on the underlying assumption that the LMWOs are less toxic than any of the individual monomeric components due to the participation of the reactive moiety in the polymerization or the reduced availability of reactive groups due to steric congestion of the long polymer chains. As the recommendation of two genetic toxicity studies at the $\leqslant$150 μg/p/d was not envisioned to be controversial with regard to LMWOs, the approach to accepting monomer data on LMWOs is on a case-by-case examination and was never approached with a global proof-of-concept analysis, as is done here.

A general weight-of-evidence scenario for examining LMWOs is provided in Fig. 1. General considerations for the safety assessment of a new polymer include determining the appropriate MW cut-off for the LMWOs, the assessment of the expected exposure, and evaluation of the safety of the material with respect to the expected exposure. If the exposure is $\leqslant$150 μg/p/d, it is then compared to genetic toxicity and carcinogenicity data on the LMWOs or their monomers, taking into consideration any new structural alerts that may be formed or destroyed during the reaction and the potential for hydrolysis and metabolism to affect the migrating fraction. Additional data beyond that of the recommended studies is also considered to determine if the safety assessment should be expanded to other endpoints. Two examples are provided in Fig. 1. In Example 1, the safety assessment is based on the weight-of-evidence of the monomer and polymer toxicity data whereas in Example 2, the safety assessment is based on the weight-of-evidence of the toxicity data of a well-characterized facsimile of the LMWOs. This Figure illustrates a small subset of the multiple approaches that can be used to assess the safety of these migrants. It needs to be emphasized that this paper deals specifically with genetic toxicity as a surrogate for potential carcinogenicity and does not take into account the broader safety evaluations that consider other endpoints (e.g., reproductive/developmental toxicity, immunotoxicity, etc.) that are also assessed when reviewing food-contact substances.

While there is limited data on the genotoxicity and carcinogenicity of polymeric and oligomeric materials, in general the analysis of the available data from public databases and internal FDA files supports OFAS' current approach to evaluating LMWOs using knowledge of the chemical reactions expected during polymerization, data on the monomers, and SAR on representative oligomeric structures to develop a weight-of-evidence-based safety analysis. For instance, the one Ames-Positive polymeric material found in the literature, methyloxirane[4] polymerized with oxirane, may have been flagged in a safety assessment as a potential carcinogen based on the Ames results. However, the structural alerting feature, the epoxide ring, is opened during the polymerization to give a polyether. The absence of the epoxide ring in the polymer and its oligomers eliminates concern for this structural alert. The formation of the ether functionalities in the polymer and oligomers can be addressed with a reduced level of concern. In cases where structural alerts are generated or maintained during the polymerization and, therefore, are present in the LMWOs, further evaluation may be recommended to ensure safety; such as actual studies on the LMWOs, or investigation of the stability of the structural alert in the LMWOs in the presence of food or gastric juices.

Although this report focused on available data, a thorough analysis of each submission must consider possible additional safety concerns in specialized cases. In most cases, the potential for breakdown of the LMWOs to their monomeric components upon ingestion is part of a discussion regarding the evaluation of possible exposure to the monomeric component(s) and the use of toxicity data on the monomer(s). Some polymeric or oligomeric materials may have the potential to biopersist or they may be absorbed or metabolized in specialized ways; an example of this occurs with perfluorochemicals. Another exception occurs when the structures of the LMWOs are sufficiently different from the monomers, such as the cyclic LMWO found in poly(ethylene terephthalate). In such cases, the monomeric data is not necessarily useful for assessing the safety of the LMWOs. For this reason, in general, there remains the need for determining the safety of LMWOs on a case-by-case basis with a thorough evaluation of the synthesis, potential degradation pathways, functional groups, and toxicity data.

As aforementioned, OFAS does, on occasion, receive data on polymers themselves or on what is referred to as LMWO extracts. In most cases, in vitro genetic toxicity data on polymers themselves are not useful for assuring the safety of a FCS due to

[4] As the epoxide functionality is converted to the less-toxic ether during the polymerization, this may be either be a spurious test result, be caused by contaminating monomers, or have some other explanation.

General Considerations for Weight-of-Evidence Polymeric Safety Assessment (1.5 – 150 µg/p/d)

- Exposure to LMWO fraction: determine appropriate MW cut-off (typically ≤ 1000 Da)
- Data on LWMOs with consideration of supporting information (extraction protocol, synthesis data, comparison to migrating species, dose of tested material)
- Data on similar LMWOs previously evaluated for safety
- Data on monomers with consideration of reactive sites consumed during synthesis
- Structure activity relationship analysis on representative dimers, trimers, etc.
- Potential for hydrolysis in food stimulant or at gastric pH and potential for metabolism *in vivo*
- Other data on LMWOs or monomer(s) as indicators of the need to address additional endpoints of toxicity outside recommended guidance for exposure level.

Example 1

Poly(alkyl methacrylates) made from one or more C12-C17 alkyl methacrylates (where the alkyl groups may be branched or linear and may be even- or odd-numbered in chain length) polymerized alone or in combination with one or more of the C18 - C22 alkyl methacrylate monomers permitted as reactants for poly(alkylmethacrylate) under 21 CFR 172.886(c)(2).

- Estimated daily intake of LMWO fraction (≤ 1000 Daltons): 13.5 µg/p/d
- Genetic toxicity data on similar, regulated polymers:
  poly(alkyl acrylate): Negative in Ames and chromosomal aberration
  copolymer of alkyl methacrylate and alkyl acrylate: Negative in Ames but high MW (110,000 Daltons)
- Genetic Toxicity Data on 'Representative' Monomers:
  Alkylmethacrylate (C12-C18) branched and linear: Negative in Ames and chromosomal aberration
- Other data (no concerns noted):
  poly(alkyl acrylate): multiple feeding studies reviewed with pivotal study being subchronic rat with a no observed effect level (NOEL) of 1000 mg/kg
  C12-C18 methacrylate monomers: subchronic studies in rats and dogs, NOEL of 500 mg/kg
- Weight of evidence indicates, based on negative findings of the genetic toxicity assays on the monomer mixture and considering the toxicological data available on compounds that are structurally similar to the FCS, no safety concerns at dietary concentration of 4.5 ppb (13.5 µg/p/d) for the LMWOs of the FCS,.

Example 2

1,3-butadiene, 2-methyl-, homopolymer, of *cis*-1,4-configuration, cyclized, as a modifier in food contact ethylene-vinyl acetate-vinyl alcohol polymers complying with §177.1360(a)(3).

- Estimated daily intake of LMWO fraction (≤ 1000 Daltons): 12 µg/p/d
- Genetic toxicity data on synthesized representative LMWO (Mw of 850 Daltons, Mn of 740 Daltons); both unoxidized and oxidized forms. Data concluded to be representative of migrating species.
- Weight of evidience indicates no safety concerns based on the the toxicological evaluation of the available data at the the estimated dietary exposures.

Fig. 1. General weight-of-evidence scenario for examining LMWOs.

concerns regarding the presumed lack of absorption of the polymer. Alternatively, if the genetic toxicity assay performed on a polymer or oligomer was an in vivo micronucleus study and toxicity was observed, the genetic toxicity assay may be seen as useful in the analysis. Data on extracts may be of limited use due to the lack of details regarding the extraction method, quantification (mass used in the analysis) or lack of proven relationship to the migrating substance. In such cases, protocols describing the extraction (such as the ISO 10993-series of standards[5]) and chromatograms relating the material extracted to what migrates to food increases the utility.

Based on an analysis of the available data, accepting toxicity data of monomers as a component of a weight-of-evidence safety decision on polymeric food-contact materials, in general, does appear to be a conservative approach for assessing genetic toxicity and potential carcinogenicity for dietary exposures ⩽150 µg/person/day. Such an analysis is assisted by also including a discussion of where the reactive groups on genotoxic or carcinogenic monomeric components may have been altered or eliminated in the polymeric material and SAR analysis of representative structures of the oligomers. Clearly, consideration of the LMWOs is an important component of evaluating the safety of polymers used in food-contact materials. When concerns exist regarding reactivity or SAR, further testing may be required; however, the use of the approaches described herein can, in general, be used to make a safety determination.

[5] http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_tc_browse.htm?commid=54508 accessed 4/13/10.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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