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# Technique for the Determination of Migratable Primary Aromatic Amines Applied to Multi-Laminate Pouches Utilizing Polyurethane Adhesives

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# TECHNIQUE FOR THE DETERMINATION OF MIGRATABLE PRIMARY AROMATIC AMINES APPLIED TO MULTI-LAMINATE POUCHES UTILIZING POLYURETHANE ADHESIVES

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Ryan Frederick Ramey
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ABSTRACT

Primary aromatic amines (PAAs) are toxic reaction products of polyurethane chemistry and form from unreacted isocyanate monomers and water. This issue is prevalent when considering polyurethane adhesive applications in food contact materials (FCM's) and food contact articles (FCAs). EU standards state that a maximum migration level of the total sum of PAAs may be no more than 10 ng $g^{-1}$ of food. Testing for migration and quantification of PAAs has not been standardized, but this research tests a published optimized method for migration testing and quantification of compounds utilizing strong cationic exchange solid phase extraction (SCX-SPE) and ultra-high performance liquid chromatography mass spectrometry (UHPLC-MS/MS) coupled with an orbi-trap detector running in positive ionization mode with parallel reaction monitoring (PRM) for the detection of 19 known PAAs. Configurations of laminated biaxially oriented polyethylene terephthalate (BOPET), Linear low density polyethylene (LLDPE), and aluminum foil were processed at Clemson University in a controlled environment utilizing a solvent-free lamination process comparing aliphatic and aromatic isocyanate-based adhesives, and the role of aluminum foil as a barrier. Pouches were made out the laminated materials and a 3% acetic acid in water food simulant was used for migration testing. Pouches were stored at 60°C for 10 days. $R^2$ values gathered from UHPLC were found to be in a linear range of 0.9976 to 1, the limit of detection (LOD) for the known PAAs ranged from 0.78 to 6.25 ng/ml. The compound aniline was the only PAA found in all tested pouches, with values ranging from 5.52 to 32.38 ng/ml, respectively. Values were reported in higher quantities with films including foil and aromatic-based adhesives, and lowest with aliphatic-based

adhesives and no foil. It was found that all pouches had a total detected value of PAAs below 10 ng $g^{-1}$, and all values of all detected PAAs after migration testing are reported. The need for recommended future work with this research is also outlined.

# ACKNOWLEDGMENTS

This research would not have been possible without the help of my cohorts, advisors, and staff here at Clemson University. I would firstly like to thank my committee: Kay Cooksey, Duncan Darby, and Patricia Marcondes for all of their guidance and knowledge they have passed onto me. Bob Bennett and Jerry Stoner, whose role in the processing of my materials and industry knowledge of equipment was invaluable and critical to this project. My fellow graduate students who helped me along the way: Steven Skrypec, Honsol Doh, Sam Kesseler, and others, not only for support in this project, but also for their empathy and stress relief when needed. My best friends Mackenzie Binns and Alice Stevens who were always a phone call away, generous, and ready to hop online and talk about our respective days. Finally, my family for always supporting me in all of my current and future endeavors.

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# CHAPTER ONE

# INTRODUCTION

Non-Intentionally Added Substances (NIAS) are a subject of concern to the food packaging industry. Primary Aromatic Amines (PAAs) are an example of NIAS that can form in polyurethane (PU) adhesives, which are commonly used in multilayer food packaging materials. Unreacted (or other free) aromatic isocyanate monomers from the adhesive may migrate through the sealant to the food contact side and can hydrolyze with moisture to create the PAA [1]. Previous studies in testing of migration through laminate films utilized samples from industry for analysis. The intent of this research is to laminate material for the purposes of making pouches for testing, this will allow for a targeted look into migration of PAAs without the introduction of unwanted variables. Solvent free lamination is used, where free monomers of the precursor components of PU, polyols and isocyanates, are coated onto a substrate and subsequently bond the films via cross-linking. This method of lamination is a becoming more adopted method in industry compared to methods that use solvent due to lower costs, decreased space needed to run, as well as environmental regulations [2].

The risk of free monomer migration from solvent free lamination may be higher compared to solvent-based lamination, where partial polymerization has already been conducted. These systems include a solvent matrix and a drying phase. Testing methods to measure NIAS, in general, have not yet been standardized due to the variety of equipment that can be used, sampling methods, food simulants, and detection methods, as well as the complexity in chemical compounds to be measured. Due to the toxic nature of PAAs, the

European Union (EU) has taken actions to restrict the amount allowable in food contact applications (EU, 10/2011) stating, “plastic material and articles shall not release primary aromatic amines in detectable quantity in food or food simulants. The detection limit is set to 0.01 mg of substances per kg of food or food simulant and it applies to the sum of primary aromatic amines released” [3]. There have been papers exploring newer methods for PAA determination and quantification, such as Pezo et al. where it was found that older spectrophotometric methods are less accurate compared to a more highly accurate liquid chromatography-mass spectrometry (LC-MS) method involving solid phase extraction (SPE) [4]. The method used for the current research follows a slightly modified method that is proposed by Aznar et al. That team used SPE of the samples, followed by the analysis of the extract by ultra-high-performance liquid chromatography tandem mass spectrometry (UHPLC–MS/MS) [5]. Another differentiating factor of the work presented in this thesis is that it utilizes an Orbitrap detector running in positive ionization mode with parallel reaction monitoring (PRM) for more accurate quantitation of the PAAs.

Strengths of the research in this thesis is the distinct knowledge of the materials and the amount of adhesive used to laminate them. Having the fresh laminate material made to industry standards being produced in a controlled and recordable environment reduces unknown errors in processing. This also allows for a more transparent analysis of migratable NIAS, specifically to PAAs.

# OBJECTIVES

**Objective 1:**

This research will utilize solvent-free technology to create laminate material, then make pouches to be used in a migration study of primary aromatic amines (PAAs).

**Objective 2:**

This research will conduct a migration test of the variables by using purified water with 3% w/w acetic acid as a food simulant. The aim is to further expand upon the methods used by Aznar et al. This is done with slight modifications to the LC-MS method to evaluate the amount of migratable PAAs by comparing samples to a standard curve of 19 known compounds [5].

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# CHAPTER TWO

# REVIEW OF LITERATURE

## 2.1 Flexible Packaging: Materials and Processing

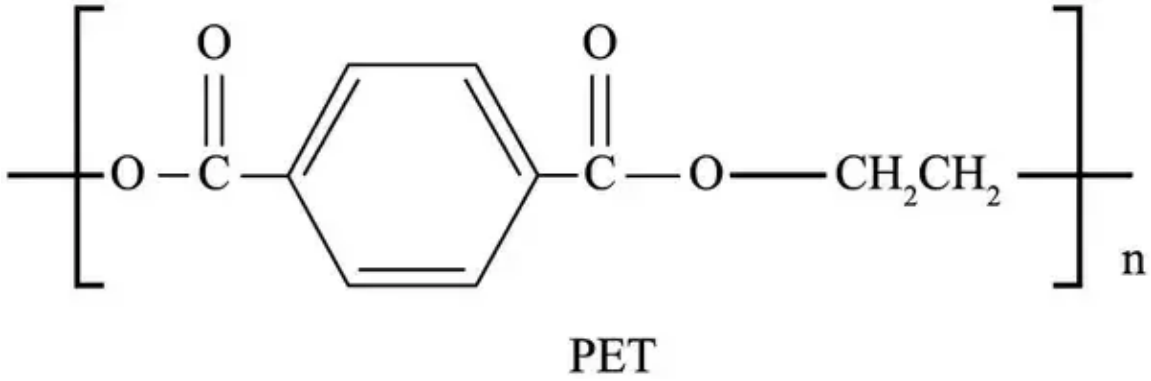
The function of a package, especially in regard to food packaging, goes beyond a single purpose. The multi-faceted expectations of a package include to advertise, entice, and inform the customer, but most importantly protect the product. Flexible packaging utilizes multiple layers of material to provide a total additive benefit for the containment of the product. Most of these layers include substrates that provide either a property that improves the shelf life of the product inside, stability to the package, sealability of a package, or provide a surface conducive for graphics applications.

Materials used in multi-layered laminates can be comprised of polymeric, paper, and/or foil substrates. Laminations are conducted with machines that take rolls of the substrates and unwind them via a primary and secondary unwinder. Adhesives are commonly used to bond the substrates and are transferred onto a primary substrate usually via a roller transfer system. These two films are pressed together and wound into its own roll. Extrusion lamination is another commonly used technique to make multiple layers of film, but for the purposes of this research, only adhesive applications will be discussed.

In this study, three unique substrates were adhesive-laminated to form two different configurations for testing: a biaxially oriented polyethylene terephthalate (BOPET), aluminum foil, and linear low-density polyethylene (LLDPE). The utilization of these materials was for the production of pouches where BOPET was the outside layer, and LLDPE was the inside food contact layer as well as the sealant layer. Aluminum foil was

introduced as a barrier material in two of the films and two different adhesives were used in total, as well. The two adhesives used are an aromatic adhesive, where primary aromatic amines (PAAs) were expected to be seen, and an aliphatic adhesive used as the control, where PAAs should not theoretically be able to form. This provides two variables for testing, where the pouches using aliphatic adhesive will act as a control compared to the aromatic adhesive, where no aromatic amines should theoretically be able to form.

PET (**Figure 2.1.1)** is a thermoplastic polymer with very good structural and thermal properties. Thermoplastics are a class of polymers that can be softened and melted by the application of heat and can be processed either in the heat-softened state (e.g. by thermoforming) or in the liquid state (e.g. by extrusion and injection molding) [1]. BOPET is commonly used in the flexible packaging industry as an outside layer in laminate films for its clarity and transparency, adhesion to inks, and inherent barrier properties. Prior to orientation, the crystalline lamellae, which are folded chains of the PET are randomly oriented. Voids in this structure of the polymer are conducive to the passage of moisture or oxygen. The stretching and heat setting in both the machine direction and cross direction arrange the lamellae in a uniform structure and "freeze" them in place, thus eliminating large voids and increasing the thermal resistance and inherent barrier property of the film [2].




PET

**Figure 2.1.1:** Molecular structure of a repeating unit of PET

LLDPE (**Figure 2.1.2**) is a thermoplastic non-polar polyolefin that is most commonly used in flexible packaging and laminates as a sealant layer. The LLDPE used in this research melts at a temperature of 134°C **[Figure B.1]** which is lower than most common structural components and outside layers in laminates such as PET (260°C), This helps create a seal at lower temperatures without damaging the outer layers and graphics.

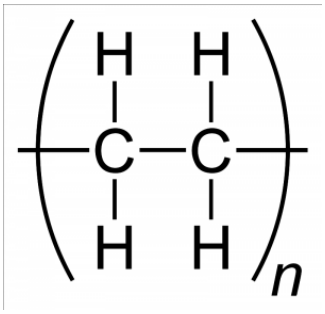



**Figure 2.1.2** Molecular structure of a repeating unit of polyethylene

LLDPE is set apart from low density polyethylene (LDPE) due to its shorter and more uniform chains branching off of the polymer, as seen in **Figure 2.1.3**.

The chains branching off of LLDPE keep the polymer from folding too compactly, making it less dense than high density polyethylene (HDPE) but the increased interstitial space within the polymer structure provides an environment for diffusion greater than compared to both LDPE and HDPE. This increased diffusion potential makes this film ideal for migration testing, as its inherent lack of barrier for lower molecular weight compounds make diffusion more likely to be seen. This is why it was chosen for this study compared to another sealant such as polypropylene.

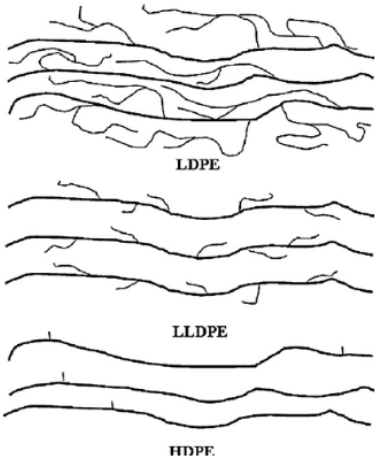



**Figure 2.1.3:** Differences inside chain dispersity between LDPE, LLDPE, and HDPE [43]

Due to the non-polar nature of LLDPE, the surface energy of the film is low (34 dyne/cm) and gives the film poor adhesion properties. The surface energy describes the energy associated with the intermolecular forces on the surface of that film, and the higher the energy, the more force that surface can apply to another substance. This requires the surface of the film to be treated in order for wettability of adhesive to occur for a better-quality lamination. Wettability refers to how a liquid interacts with and spreads across a

solid surface [3] and that can be measured by looking at the contact angle. The contact angle is the measurement of the angle a drop of liquid makes against the surface of a film at a given temperature. A low surface energy on a film causes liquids to have a high contact angle (>90°) and not spread across the surface of a substrate. A contact angle of 0° would be perfect wetting and spread across a substrate fully [3].

Surface treatment for this study was accomplished with a corona discharge device. A high electrical field (400-2000W) is produced by the machine via exposing the film to a strong voltage. This electric field causes the atmosphere around the film to become ionized, in which excited molecules in the air collide to create free electrons that bombard the surface of the substrate. This roughens up the polymer structure because free radical oxygens rip hydrogens off of the PE chain, which leads to a higher surface energy [3]. The measurement for surface energy is the dyne level (dynes/cm) and a product called a dyne pen can be used to measure this. These products come in a multiple set which contain solutions of a specific surface tensions. These pens are drawn across the surface of a film, and if the liquid beads up, the surface energy of the film is lower than compared to the surface tension of the pen. Typical levels of untreated LLDPE range around 20 to 32 dynes/cm, and in order to ensure proper wetting for lamination, the films' surface energy needs to be raised to at least 44 dynes/cm [4]

### 2.2 Adhesive Applications

There are four main forms in which industries can supply an adhesive: Solution, suspension, emulsion, or 100% solids (solvent-free) application. Where applications that

involve solutions, suspensions, or emulsions in solvents or water, a drying variable is introduced, and this usually involves special equipment and time. Along with those, the cost of the solvent or water used is additive in the operations cost. Clemson University has the capabilities to run solvent based and solvent free laminations in the DuPont laboratory, and for this research solvent-free was chosen. More information regarding lamination and flexible packaging is available in books authored by Dunn and Morris [40][41].

In a process where solvent is utilized, some of the polyol and isocyanate components of a polyurethane adhesive are pre-reacted and mixed with solvent in order to lower the viscosity. As a consequence of pre-existing polymerized chains, the green bond is reasonably high. The green bond is the immediate peel strength of the lamination after processing [5]. Drying is a key component in solvent lamination also, and the heat during the drying of solvent in-line with the machine also provides an environment for increased polymerization to occur.

Solvent-free adhesive involves a two-component adhesive set-up, but there is limited to no pre-polymerization. Since there is no solvent used in 100% solids lamination, there is no need for a drying apparatus. Limited use of pre-polymerized material, the initial molecular weight of the adhesive is low. Green bonds of laminates produced from 100% solids adhesives are typically 0 g/in [5] which means the laminate provides no resistance to being separated. The consequence of a low green bond is a required cure time prior to further processing or use of the laminate. In general, solvent based laminations cure faster than solvent-free.

One of the reasons why the shift into solvent free adhesives has been somewhat slow is because the operational equipment for these applications are different, and new machines would need to be purchased and installed. The slower cure time in production and the initial investment in machinery may not be a suitable decision for some manufacturers.

Adhesives sold in the solvent-free market include epoxies, silicone-based, methyl-methacrylates, and urethanes [6]. This research focused on urethane-based adhesives for its use in the food industry and its potential to produce aromatic amines.

### 2.3 Polyurethane Adhesives

Polyurethane (PU) chemistry was first studied by Otto Bayer, a German chemist, in 1937 with the company IG Farben. His research had expanded drastically in response to World War II. Rubber was becoming scarce in the time of war and alternative materials were desperately needed [7]. Previous research from Bayer a few years earlier involving one of the building blocks for polyurethane, toluene diisocyanate (TDI), was utilized to form one of these rubber alternatives known as "Perlon U" which was used for brush bristles and as a coating for vehicles [8].

Polyurethane adhesives are also known as reactive adhesives. They function on the basis of combining two low molecular weight compounds and, through a curing process, a polymerization reaction occurs that increases the molecular weight (and cross-links) the compounds as shown in **Figure 2.3.1**. These linkages form a growing polymer chain, and the increase in molecular weight of the chain leads to a stronger bond. One of the main

components of this reaction are diisocyanates, and the two main forms utilize either an aromatic or aliphatic structure.

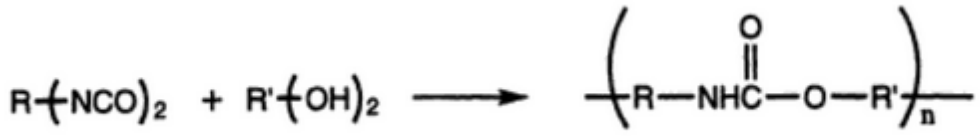



**Figure 2.3.1** Polymerization reaction of an isocyanate and polyol to create a urethane linkage

Aromatic isocyanates are more ubiquitous in industry because they are more reactive and less expensive compared to aliphatic isocyanates. The most common aromatic isocyanates used in industry are MDI (methylene diphenyl diisocyanate) and TDI (toluene diisocyanate) [9]. Isocyanates are identified by the NCO termination on either end of the molecule. These are unsaturated bonds, and the main reactive force in the PU chemistry they encounter is when met with hydroxyl groups, such as those on polyol compounds.

Polyols are the second component involved with the PU chemistry and are molecules that are predominantly hydroxy-polyethers, but some are forms of hydroxy-polyesters. The polyol, and number of hydroxyl groups on them, are important to PU formation as this is what controls the degree of cross linking in the material. Cross linking is important to control since it will dramatically affect the mechanical properties of the polyurethane. If the PU crosslinks to a very high degree, this will cause the PU to become very rigid and act as a thermoset polymer. For adhesive purposes, this may not be advantageous so the polyol would need to have only one or two hydroxyl groups to prevent too much cross linking.

Additives are ingredients added to the main PU chemistry to provide specific attributes to the adhesive. In general, these additives may be used more in non-adhesive applications of polyurethanes, such as foams. Additives include catalysts, cross-linking extenders, fillers, plasticizers, pigments, etc. and are usually left as trade secrets in industry for use in different grades of adhesives.

According to a life cycle analysis conducted by Iowa State University, after polyurethane adhesives are fully cured in films, they may be considered non-toxic and safe. Though they are deemed non-toxic at this point, during manufacturing, hazardous materials may be introduced into the environment such as solvent vapors from drying, and side products such as aromatic amines may be formed [10].

### 2.4 Migration

The transfer of chemical contaminants from food contact materials (FCM) into food is called migration [11]. This phenomenon is of particular relevance when considering low molecular weight compounds (<1000 Da). Compounds that migrate through a material are called “migrants” and can include residual monomers, solvents, residual catalysts, and other polymer additives [12].

The mass transfer of compounds that diffuse through a polymer material are of great practical importance to modern industry. As packaging and technology grow, the complexity of these systems leads to a challenging approach to understanding how chemicals may penetrate through to a food contact layer, and how the organoleptic

properties of that food may be affected. Many factors contribute to the extent of chemical partitioning including time, temperature, surface area, and physicochemical properties. Dr. Bach at the University of Lorraine conducted a study on PET water bottles where it was seen that increased temperatures and storage time increased the concentration of formaldehyde and acetaldehyde seen in their samples [13]. Heat adds energy to the reaction, and given enough time, more compounds will migrate.

These types of variables become of particular significance when considering the packaging matrix. Inert packaging such as ceramics and glass may only be susceptible to issues of migration due to contaminates already present on the food contact side of the package. The chemical structure of these materials, which restricts single atoms from transferring through, makes diffusion not possible to occur from outside the package to the inside [11]. Diffusion can be defined as a mass transfer phenomenon that causes the distribution of a chemical species to become more uniform in space as time passes [14]. When considering possible migrants in packaging, such as monomers from an adhesive in a laminate material, a higher concentration on one side of a layer may diffuse through an interstitial void in the film to an area of lower concentration to create an equilibrium. In the case of this research, that layer is a food contact material.

Materials that are considered to be non-inert, or reactive materials, are substrates such as plastics and paperboards. Contrasting to glass and metals, polymer and paper materials have relatively larger pore sizes within the matrix of the material. This allows for the possibility of chemical migration of compounds from outside the substrate to the inside layer. Polymer dispersity and crystallinity plays a role in this, as the more amorphous and

low density the polymer, the more susceptible the film is to migration such as the LLDPE used in this study. Barrier materials, such as foils or other polymer substrates, may be used in laminate structures to reduce migration. Aluminum foil is a metal that has been processed into a thin sheet and provides an excellent barrier to light, water, oxygen, and also provides structural rigidity [15]. Foil does add significant cost to the package, and ultimately the customer, due to the cost of the materials and extra processing of that package. The use of foil in this research is to test for its effects on migration in relation to adhesives, and whether it has a positive or negative against migration if laminated directly to a sealant layer.

It is important to consider migration in packaging development. The contamination a migrant may introduce has the ability to cause damage to the quality of the food such as oxidation or color degradation. In other cases, the consumer may be at risk as well if the compounds that migrate pose a concern to one's health.

The PAAs chosen for this study were selected based upon a previous study by Aznar et al. [1] where a similar migration study into PAAs were conducted. All compounds, as seen in **Figure 3.2.1**, belong to the Cramer class III level of toxicity. The Cramer rules classify compounds in three groups depending on their toxicity: low toxicity (class I), intermediate toxicity (class II), and high toxicity (class III) [39].

## 2.5 Analytical Methods

Although there are no standardized testing methods for primary aromatic amines (PAAs), there has been a multitude of research conducted to attempt optimizations on

quantification and identification of migratable PAAs in FCM's. This research follows steps written by Azner in which food simulants are used to conduct a specific migration test in temperature-controlled conditions, and samples purified via solid phase extraction (SPE), followed by injections into an ultra-high performance liquid chromatography system coupled with a mass spectrometer (UHPLC MS-MS) [16].

A specific migration test focuses on targeted compounds with a known toxicity, such as the 19 PAAs chosen for this research. The use of the food simulant: purified water containing 3% (w/v) acetic acid, is determined by its use in literature and by EU regulation set out in EU 10/2011 for simulating foods with a low pH. This was chosen for this research since it represents the worst case for the migration of aromatic amines. The EU regulation also states storage and temperature conditions for migration testing: "60°C for 10 days shall cover long term storage above 6 months at room temperature and below" (EU-10/2011) [17].

Pezo et al. [18] also conducted a migration study using laminated food packaging films and analyzed samples for the presence of targeted PAAs as well as a general sweep for NIAS, respectively. They performed a qualitative analysis for the presence of PAAs and tested 18 different pre-made laminate film configurations utilizing some different PU adhesives. They do not state the specific brand nor whether the adhesive used was an aliphatic or aromatic based adhesive as they were stated as confidential, but they did find compounds of aliphatic amines from their results. With this study, a spectrophotometric method and a chromatographic method were used and compared. Conflicting results from the two methods resulted in more robust testing which confirmed that compounds with

similar chemical characteristics as PAAs skewed the results of the spectrophotometric method and inflated the results. With the qualitative results, they confirmed the presence of 40 compounds that may be considered as NIAS in all 18 of the laminates they tested. Due to the issues that were observed with the spectrophotometric method, which was noted to be due to lack of sensitivity and reliability since the method is limited by wavelength restrictions and poor reproducibility, this method was not considered for the research of this paper.

Solid phase extraction (SPE) is a critical clean up and purification technique used to increase the accuracy of the method by isolating target analytes from a sample by leveraging physical and chemical properties such as molecular weight, polarity, acidity, or net charge of the selected compounds [19]. A solid media, or stationary phase, acts as a chemical filter that is housed in a small cartridge. This solid phase captures either desired or undesired compounds due to chemical affinities of the substrate reacting to the analyte, and can be rinsed with an eluant, or mobile phase, to release analytes to be captured for analysis.

Aznar suggests the use of a strong cation exchange SPE (SCX-SPE) method due to the positive nature of the PAAs in acidic solutions. The cartridges used in that study are the same as used in this study and are polymetrically coated with benzyne-sulfonic acid. This provides a selective extraction of cationic compounds, and since PAAs become cationic when in acidic solutions. it becomes an efficient method for targeted extraction. In order to elute the PAAs trapped in the media, methanol with 5% $NH_3$ solution was used

because the basic character neutralized the PAAs allowing their elution, and due to the methanol, it had also an elution effect over the possible hydrophobic interactions [18].

When considering the detection methods for aromatic amines, UHPLC-MS/MS has been found to be more effective than gas chromatography mass spectrometry (GC/MS). A study where aromatic amines were tested in cosmetics compared the two analytical methods. The GC/MS system in the authors' laboratory resulted in lower accuracy compared to the LC system, partly due to the poor stability and high volatilization of AAs which negatively responds to the heat that GC requires [20]. For these reasons, and due to the lack of any one standardized method, the SPE of samples followed by UHPLC-MS/MS method for determination was adopted for this study.

Ultra-high-performance liquid chromatography is a powerful analytical tool that is used to separate compounds in a sample. This is done by pumping the sample under high pressures using a liquid (mobile phase) which is usually a mixture of solvents and water to pass through a column (stationary phase). The column is made with silica particles which can be packed to have varying pore sizes to exclude specific molecular weight compounds and can be modified to be either polar or non-polar based on the specific application. This allows for the targeted attraction of analytes in samples which allow them to be eluted out of the column at different rates, or retention times, and be sent for further analysis via a detector.

One change from the Aznar method is that the LC-MS system used for this study also utilized a tandem orbitrap mass analyzer. An orbitrap mass analyzer works in tandem mass spectrometry (MS/MS) where compounds that are eluted from a chromatography

machine are sent for quantification. Heated electrospray ionization (HES-I) was utilized for this research, where the liquid sample compounds from the LC are exposed to a very high voltage to create an aerosol and become ionized. The entire machine operates at a very high vacuum to allow for the flow of ions with an inert gas, usually helium or nitrogen. The ions are further separated according to their mass-to-charge ratio (*m/z*) through the use of a quadrupole. A quadruple is a parallel set of four molybdenum rods that has an oscillating electric field applied to it. The trajectories of ions flowing through the quadrupole are affected by the electric field based on their molecular weight, and the machine is able to capture specific ions that have a particular trajectory path in the quadrupole. From here, the selected ions are sent into a collision cell where they are fragmented with atoms of an inert gas at high velocity. These ions are accelerated by placing an electronic potential on the atoms to increase the ion kinetic energy known as the collision energy (CE) and is measured in electron volts (eV) [38]. Fragments of the ions are sent into the orbitrap from this point for mass detection. An orbitrap relies on the inner and outer electrodes which are axially symmetrical to trap ions in a rotational field. The radial potential is gained by an applied DC voltage to the electrodes and is maintained via centrifugal force. This electrostatic potential is described in a paper by Makarov, who invented the orbitrap, to be quadrolograthmic [37]. Ion fragments trapped in this field can be detected by the rotational frequency of the ions. The rotational energy of the ions creates a current and are detected to create a mass spectrum.

This set-up allowed for the use of the machine to run in parallel reaction monitoring (PMR) mode instead of the previous studies, which ran in multiple reaction monitoring

(MRM) mode. MRM is a method used in tandem mass spectrometry in which an ion of a particular mass is selected in the first stage of a tandem mass spectrometer, and an ion product of a fragmentation reaction of the precursor ion is selected in the second mass spectrometer stage for detection. PRM is the analyses in which the full fragment ion spectrum of each precursor in a target list is recorded continuously throughout the entire LC separation. This allows for the detection of more fragmentation and provides for more accurate quantitation of PAAs [21].

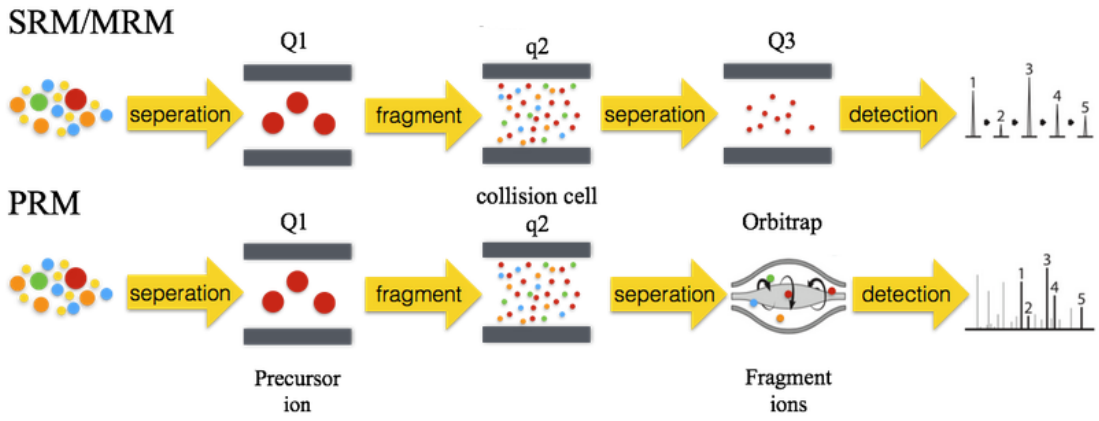



**Figure 2.5.1** Representation of the differences between MRM and PRM mode [42]

## 2.6 Regulatory factors

The U.S. Food and Drug Administration (FDA) chapter 21 Code of Federal Regulations (CFR) sets out multiple provisions covering food contact surfaces (FCSs). An FCS is defined as "any substance that is intended for use as 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 such food" (21 CFR 170.3(e)) [22]. The FCR

suggests that any FCS that may reasonably expect to have migration due to its intended use as a food contact article (FCA), that it must comply with its legal requirements recognized by the FDA. The FDA considers all NIAS as within their definition of "impurity", thus the term is not legally recognized, but they have provisions concerning these in 21 CFR 174.5, and direct impurities originating from the FCS in 21 CFR 170.3(i): "Any FCS shall be of a purity suitable for its intended use"[23][24][25][26].

The use of adhesives in FCMs are also mentioned in 21CFR. The FDA states polyurethane adhesive are approved for use in lamination structures that are intend for food use if the adhesive is not the main food contact material, and only if it contains chemicals listed in the regulation (FDA 21CFR 175.105) [27]. The FDA recommends the submission of information of possible major impurities and side reactions when submitting for regulatory standards [28].

Contrasting to the United States, the European Union (EU) does recognize the term NIAS. The EU sets out specific regulations regarding FCM safety stemming from the framework regulation and requires that the FCM manufacturer ensures NIAS safety (EC No 1935/2004) [29]. This consequence of the framework regulation implies that the safety of NIAS needs to be assessed. As mentioned in the next section, the complete analysis of all NIAS is very impractical and standardizations of analysis for NIAS is nonexistent, making this topic a challenge for manufacturers.

PAAs are considered to be NIAS but are well known contaminates which have specific regulations regarding migration.

"Plastic material and articles shall not release primary aromatic amines in detectable quantity in food or food simulants. The detection limit is set to 0.01 mg (10 μg) of substances per kg of food or food simulant, and it applies to the sum of primary aromatic amines released." (EU No 10/2011) [17]

International authorities recognize the importance of a risk assessment for NIAS but have not provided official guidance so far, making it difficult to enforce and comply with the legal requirements. In 2016 the European parliament emphasized the importance of further research on NIAS to enable their risk assessment [30]. Due to the EU's efforts to further the assessment and safety of NIAS, this research utilizes standards based on EU compliances as opposed to some non-existent FDA approaches.

### 2.7 Non-Intentionally Added Substances

Non-intentionally added substances (NIAS) are chemicals or particulates the exist within an FCM and have not been added for a technical reason in processing. It is possible for NIAS to migrate into food, but due to the complex nature of the process, it is difficult to predict and control. How NIAS form within a package is just as complex. Contaminates, degradation products, and neoformed compounds, are all sources for NIAS formation [31].

When considering packaging that is comprised mostly of polymer films, degradation products are one of the more frequent pathways to the formation of NIAS. Processes that incur within manufacturing such as high temperature and irradiation for the purposes of sterilization may cause the polymer or the additives within the film to break down [31]. When these compounds break down, low molecular weight compounds or

monomers may form, and due to the higher diffusion potential, the risk of migration through the interstitial space between polymer matrices increases.

The main focus of this research revolves around neoformed compounds. These are chemicals that react within the package, usually additives or free monomers of adhesives, and under certain conditions form new and possibly hard to detect compounds [32]. Taking into consideration the extreme complexity and variety of chemical pathways that exist, the targeted analysis of NIAS in all packaging is nearly impossible. A targeted analysis refers to the qualitative observation of specific compounds, as opposed to a general sweep for all chemicals in a sample. Predicting some NIAS formation may be possible with knowledge of chemical processes and manufacturing experience, but detecting all compounds that may form considering contaminates, side reactions, and breakdown products, makes total NIAS quantitation impractical and unrealistic. Quantification of NIAS is also challenging because analytical standards are usually missing [32]. A risk assessment, which is the process of identifying potential hazards and analyzing what could happen if that hazard occurs [33] is vital prior to screening NIAS. Regulatory obligations and concerns of toxicity are factors in this decision since the hazards in question deal with food and human consumption.

Dr. Cristina Nerin and the members in her lab from the University of Zaragoza are pioneers in research regarding NIAS and PAAs. She lays out the challenges of identifying NIAS in her paper: “The challenge of identifying non-intentionally added substances from food packaging materials: A review” [32]. From this review she states how the scale of identifying unknown NIAS is great and explains the current processes available for testing.

The biggest challenge, she writes, is knowing the proper procedure for analyzing possible migrants. Having in-depth information about the sample, materials, and manufacturing process provides important background information to narrow techniques that should be utilized.

There are many papers which outline specific testing for one particular NIAS, such as bisphenol-A in cans, and in more general cases such as photo-initiators, phthalates, and antioxidants in other food contact scenarios. This research focuses on not any one specific PAA, but a spectrum of PAAs that may form within a package.

### 2.8 Primary Aromatic Amines

Primary aromatic amines (PAAs) are a broad class of organic compounds in which basic configurations consist of an aromatic ring with an amine group, aniline, to a complex set of rings with multiple amines [34]. The main way PAAs may form in food packaging are from side product reactions of PU adhesives, which categorizes PAAs as NIAS. The full polymerization of polyol and isocyanate monomers requires a specific ratio of each compound to react together, but if there is a miscalculation in the ratio or if the laminate is left uncured, free monomers of isocyanate will exist. Monomers of isocyanate have a low molecular weight and have the ability to migrate to the FCM and react with water to form aromatic amines [34]. It is known that PAAs can further react with more free isocyanate monomers to form poly-urea. This is a non-toxic compound which is a more ideal alternative to PAAs but due to urea's melting temperature 232°C, the sealing properties of

the film may be compromised [35]. This leads manufacturers to make sure all PAAs are reacted out by allowing the rolls to cure past the suppliers recommended curing time.

Studies such as the one conducted by Campenella et al. suggest that this may not be a perfect solution to eliminating all PAA concerns if there is any post treatment of the package. Depolymerization may not be a major concern, but cleavage of biuret and specifically allophanate linkages due to thermal stress may lead to re-formation of free isocyanates [35].


**Figure 2.8.1**: Reaction mechanism between an isocyanic monomer and a water molecule to yield a primary amine

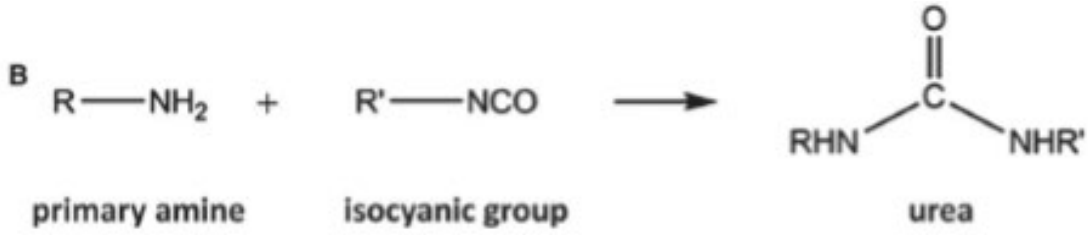



**Figure 2.8.2:** Reaction mechanism of a primary amine and an isocyanic monomer to yield a urea

Aromatic amines are toxic substances and are assumed to be carcinogenic in humans. Ingestion of these substances may cause a complex pathway of metabolic and conjugation reactions in the human body which may lead to carcinogenesis. It has been seen in rats that highly electrophilic nitrenium compounds result from the PAA conjugation

pathway, shown in **Figure 2.8.3**, and these are known to further react, as well as cause adducts on cellular macromolecules including DNA [36]. Though there are no direct studies in regard to human physiology, these tests in animals correlate to human bodily function, and it is highly suggestive that these effects will be similar.

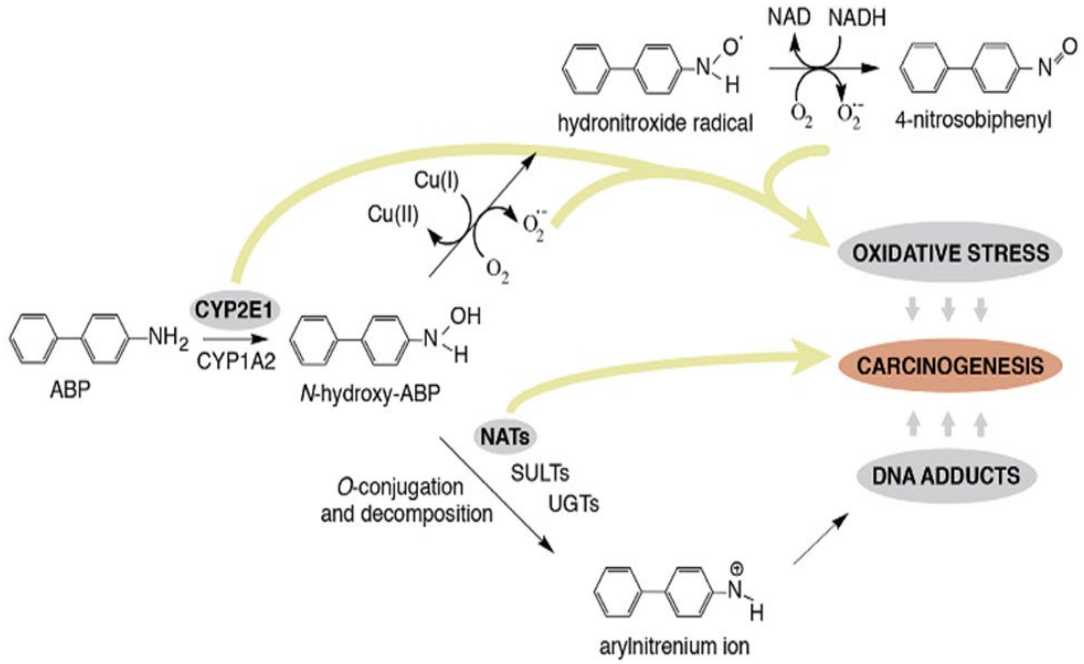



**Figure 2.8.3:** Conjugation pathway of 4-aminobiphenyl in rat liver leading to liver carcinogenesis [36]

The most effective way to prevent the formation of PAAs in packaging is to use a non-aromatic isocyanate in the adhesive formulation. The use of aliphatic isocyanates is typically seen as unprofitable in industry, though, due to the high cost compared to pure aromatic systems. Aliphatic systems are not ideal in industry because the lower reactivity requires a longer polymerization period, and this requires companies to extend storage time for curing of laminated rolls. This causes through-put extensions due to the aforementioned logistical impediments, and ultimately increase further the cost of this system compared to

aromatics [34]. Because of this, in applications where aromatics are used, a risk assessment associated with the formation of PAAs should be conducted and considered critical to the development of the package.

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CHAPTER THREE

MIGRATION OF PRIMARY AROMATIC AMINES IN MULTI-LAMINATE POLYOLEFIN / POLYURETHANE, STRUCTURES

## 3. Materials and methods

### 3.1 General flow of procedures

Materials for lamination were obtained from commercial sources. Analytical standards of PAAs and material for analysis were purchased. Stock solutions of all PAAs were made and used for further dilution for use in a standard curve and system suitability test **Table A.2**.

Solvent-free adhesive lamination of films was preceded by the corona treatment of LLDPE. PET and foil were laminated first and then cured. A second pass was then conducted to laminate to LLDPE. BOPET and LLDPE were also laminated without foil. All laminations were conducted according to the materials' specifications i.e. adhesive basis weight, mix ratios, nip temperature and cure times.

Rolls of film were slit to fit the pouch making machine, and pouches were made and trimmed to have an inside area of 10 x 10$cm^2$. Twelve pouches from each roll were used as replicates for each structure. The pouches were filled with food simulant and sealed, then placed in a temperature-controlled chamber for 10 days.

After 10 days, the pouches were decanted into cleaned and then sterilized analytical jars for use in the solid phase extraction (SPE) process. Statistical analysis was conducted with the results and is detailed in the results section **Table 4.2.3.**

### 3.2 Solvents and reagents

DSC-SCX C18 cation-exchange solid phase extraction (SPE) cartridges (500mg/3mL) were purchased from Supelco (Bellefonte, PA, USA) and a 'BAKER'-10 manifold system was used from J.T Baker Chemical Co. (Phillipsburg, NJ, USA).

PAAs of analytical grade were purchased from Sigma-Aldrich (Milwaukee, WI, USA) and Fisher Scientific (Pittsburg, PA, USA).

HPLC grade methanol, glacial acetic acid, and ethyl acetate were purchased from Fisher Chemical (Fair Lawn, NJ, USA) and 4% ammonia in methanol from TCI America (Portland, OR, USA). Ultra-pure water was obtained via use of a Purelab Flex. water purification system from Veolia Water Technologies (Paris, France).

A list of all PAAs used are shown in **Table 4.2.1**. Individual solutions of PAAs were made into 10,000 ppm concentrations prepared in methanol for storage.


**Figure 3.2.1:** Analytical standards of PAAs

### 3.3 Solvent-free lamination

*3.3.1 Films and foil*

Materials meant for use in a multi-laminate structure were collected. Biaxially oriented polyethylene terephthalate (BOPET) (12000ft) of 48Ga thickness 24CTN Hostaphan® was donated from Mitsubishi Polyester Films (Greer, SC). Linear low-density polyethylene (LLDPE) (12000ft) of 2 mil thickness - DOW ELITE™ 5960G was donated from DOW Chemical (Midland, MI). Aluminum foil (9000ft) of 0.5 mil thickness was purchased from All Foils USA (Strongsville, OH).

*3.3.2 Adhesives*

Two different polyurethane adhesives (one utilizing aliphatic chemistry and one utilizing aromatic chemistry) were donated from DOW Chemical (Midland, MI). Information about these adhesives are presented in **Table 3.3.1.**

**Table 3.3.1:** Adhesives used and their corresponding mixture specifications

| | **Isocyanate** | **Polyol** | **Mixture ratio** | **Pot life** |
|---|---|---|---|---|
| **Aromatic** | Pacacel L75-191 | CR-89 | 10:6 | 30 minutes |
| **Aliphatic** | Mor-Free 1390A | CR-33 | 1:1 | 15 minutes |

The specific isocyanate and polyol compound(s) used in these adhesives are proprietary and considered trade secrets.

*3.3.3 Corona treatment*

To ensure proper wetting of adhesive to the film, ACCU DYNE TEST™ dye pens from Diversified Enterprises (Claremont, NH, USA) **Figure 3.3.1** were used to measure the surface energy of the LLDPE following ASTM D2578-09 [3]. A Varyflex VF530F1 press (Omet, Lecco, Italy), equipped with a Corona-Plus TF-415 corona treater (Vetaphone, Denmark) was used to corona treat six rolls of LLDPE film. The treatment section of the press is shown in **Figure 3.3.2.** The average post-treatment surface energy (dyne level) of the LLDPE rolls was 53 dyne/cm.

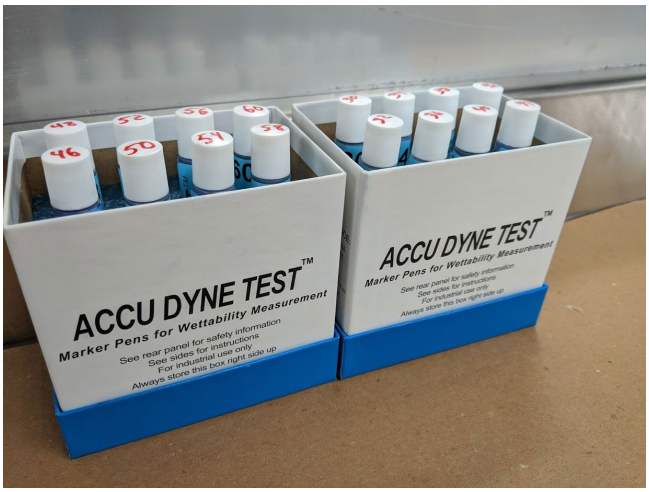



**Figure 3.3.1:** Accu Dyne Test™ pens

**Table 3.3.2:** Specifications for corona treatment

| Primary unwind material | Material Core (in) | Material Width (in) | Corona Discharge Treatment Side | Corona Discharge Treatment Watts | Dyne Level Before Treatment (dyne/cm) | Line Speed (ft/min) |
|---|---|---|---|---|---|---|
| **LLDPE** | 3 in | 14 in | Out | 400 Watts | 34 | 200ft/min |

**Table 3.3.3:** Post corona treatment results

| **Length of Roll** | 1634ft | 1991ft | 2004ft | 1980ft | 2040ft | 2006ft |
|---|---|---|---|---|---|---|
| **Dyne level after treatment (dyne/cm)** | 55 dyne/cm | 53 dyne/cm | 53 dyne/cm | 54 dyne/cm | 52 dyne/cm | 52 dyne/cm |

**Figure 3.3.2:** Vetaphone Corona-Plus type TF-415 corona treater installed on a Varyflex Omet VF 530F1 printing machine

*3.3.4 Solvent free lamination*

A solvent-free lamination machine from Polytype LTD. (Fribourg, Switzerland) series number 612'0614 was utilized to laminate the layers together (**Figure 3.3.3)**. **Table 3.3.5** expresses the configurations of each lamination. "**ARO"** represents pouches with aromatic adhesive and **"ALI"** represents the pouches with aliphatic adhesive, with "**-F"**

indicating aluminum foil in the structure. Two rolls, for a total of 6000 ft. of laminate material were produced for each variable, for each adhesive.

The laminations which included a foil layer made in two passes through the machine. A first lamination of BOPET to foil was made, where BOPET was on the primary unwind, and foil on the secondary. A second pass was then made where the BOPET/Foil laminate was on the primary and LLDPE on the secondary. All conditions for lamination are expressed in **Table 3.3.4.** The room where laminations occurred was humidity controlled to an average RH of 48%. For the laminations of BOPET/LLDPE, the BOPET was on the primary, and LLDPE on the secondary. In between each run, the machine was thoroughly cleaned, and any residual adhesive was removed from the roller surfaces with the use of acetone. Adhesive was added during laminations in batches. Pot life of the adhesives are listed in **Table 3.3.1**. Around 150g of total adhesive was mixed for each batch and then added to the current adhesive pool on the roller system at that time. If the adhesive appeared to get too cloudy during lamination, it was removed and replenished with fresh adhesive. The finished rolls of film were set to cure in room temperature conditions at times equal to or longer than recommended. Manufactures recommendations for the aliphatic adhesive states 10-14 days to fully cure, and the aromatic adhesive suggests 2 days at room temperature.


**Figure 3.3.3:** Polytype LTD. (Fribourg, Switzerland) series number 612'0614 Solvent-free lamination machine

**Table 3.3.4:** Solvent Free lamination machine conditions

| **Solvent-free lamination machine conditions** | |
|---|---|
| Nip temperature | 55$^{oC}$ |
| Adhesive gap | 0.001 in |
| Transfer gap | 0.001 in |
| Primary torque | 8-10in/lbs |
| Secondary torque | 2-3in/lbs |
| Line speed | 60% |

**Table 3.3.5:** Designation of names for lamination variables

| **ARO** | **ALI** |
|---|---|
| BOPET/ADH[1]/LLDPE | BOPET/ADH[2]/LLDPE |
| **ARO-F** | **ALI-F** |
| BOPET/ADH[1]/FOIL/ADH[1]/LLDPE | BOPET/ADH[1]/FOIL/ADH[2]/LLDPE |

* ADH[1] = Pacacel ADH[2] = Mor-Free

*3.3.5 Basis weight*

Basis weights were calculated at the start and end of each lamination run according to ASTM 2217 (Standard Practice for Coating/Adhesive Weight Determination) [4].
This was done to ensure that an even and proper amount of adhesive was coated onto the film during each lamination, and to ensure that the manufacturers' recommendations for the products were being met. Samples of freshly laminated film were cut in three places across the roll width using a 3.08sq/in stencil. Each square was weighed to the nearest ten-thousandths gram using an APX-60 analytical balance (Denver Instruments, Bohemia, NY). The squares were peeled apart, and ethyl acetate was used to wash away fresh adhesive off the layers. The samples were dried and reweighed.

The following calculation (**Figure 3.3.4)** was used to determine the basis weight of the adhesives:

| **(BW)(#/ream) = (Sample Weight with Pre-wash – Sample Weight Post-wash) * 100 #/ream** |
|---|

**Figure 3.3.4** Adhesive basis weight formula

Basis weight amounts of each roll of laminate are listed in **Figures 4.1.1 & 4.1.2**

## 3.4 Pouches

### *3.4.1 Formation of pouches*

Pouches were made using a model FSD-600SZ three side seal stand-up pouch machine from Shanghai Gaoqin machinery limited corporation (Shanghai, China). It is shown in **Figure 3.4.1**. The machine ran at a speed of 25 pouches per minute, with a sealing temperature of 112°C and a dwell time of 0.5 seconds. The pouches' original dimensions were 28.73cm X 12.62cm with an inside seal width of 10cm. The machine ran for 30 minutes for each roll and pouches that showed defects were discarded.

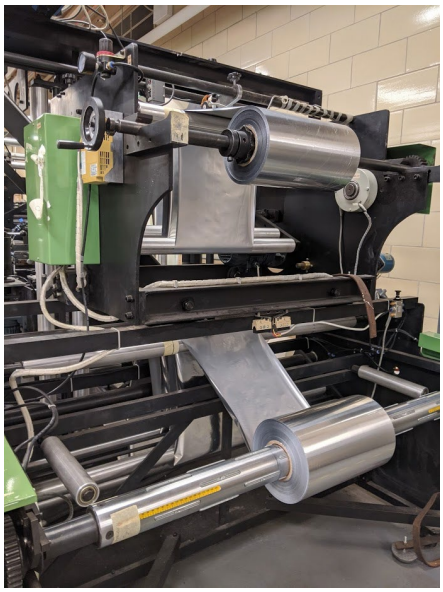


**Figure 3.4.1:** FSD-600SZ three side seal stand-up pouch machine – input end of machine

**Figure 3.4.2:** FSD-600SZ three side seal stand-up pouch machine – output end of machine

**Figure 3.4.3:** Blanks of pouches before sealing

A total of 12 pouches of satisfactory quality were randomly selected from each roll for a total of 48 pouches. The seal strength of the pouches was tested and validated with a MECMAN series 1100 (Sweden) **Figure 3.4.4** seal strength burst testing device following ASTM standard F1140-2013 [5]. The mechanism of failure was tested. The pouches were shown to burst before the seal could fail, which indicates good seal quality.

**Figure 3.4.4:** MECMAN series 1100 seal strength burst testing device

*3.4.2 Pouch filling*

Purified water (100mL) containing 3% (w/w) acetic acid for use as a food simulant replicating acidic foods in was measured and placed into each pouch. Pouches were sealed using an impulse heat sealer (Model 9MS #1091, Toyo Jidoki CO., LTD, Tokyo, Japan) **Figure 3.4.5** at 135°C sealing temperature with a heating time of one second

and cooling time of one second. The pouches were sealed making the inside dimentions of the pouches was 10cm x 10cm$^2$ and any excess was trimmed and then discarded.

**Figures 3.4.5:** Set-up for sealing pouches **3.4.6:** Sealing of pouches

*3.4.3 Conditioning of samples*

According to European Union guidelines (10/2011), a conditioning of samples for 10 days at 60°C in a temperature-controlled chamber was used to replicate an accelerated simulation of 6 months at room temperature for migration testing [6]. A Thermotron SM-8C temperature-controlled chamber (Holland, Michigan, USA) (**Figure 3.4.7)** was used and kept at a relative humidity of 50%. Pouches were flipped halfway over through to maximize surface area coverage. After 10 days, the pouches were removed and decanted into individual glass jars, labeled, and kept in refrigerated conditions until further testing was conducted.


**Figure 3.4.7:** Thermotron SM-8C temperature-controlled chamber

### 3.5 Solid phase extraction (SPE)

The SPE step of the procedure followed the procedures according to Aznar et al. [1] Cation exchange SPE cartridges were placed upon a Baker-10 SPE system vacuum manifold as seen in **Figure 3.5.1,** and a slight vacuum was pulled to allow the solutions to flow though the matrix inside the tubes. The cartridges were first conditioned with 2mL of MeOH and then 2mL of purified water containing 3% (w/w) acetic acid. Tubing was hooked up to the jars containing the 100mL of the sample collected from the pouches and was constantly run through the cartridges via vacuum at around 1.5 mL $min^{-1}$. A wash step of the cartridges after the sample finished running was conducted using 2mL of purified water containing 3% (w/v) acetic acid. The tubes were then placed under a stronger vacuum until the matrix inside was dried. Elution of the target analyte (PAAs) was

conducted using methanol that contained 4% ammonia (v/v). Eluting solvent (1 mL) was pulled through the tubes via gravity (not vacuum) and collected, then discarded. A second mL of eluting solvent was then pulled through the tube via gravity and then collected, and this was kept for MS/MS analysis.

An internal standard of 4-aminoazobenzol was added to all of the sample extracts before analysis to check reproducibility.

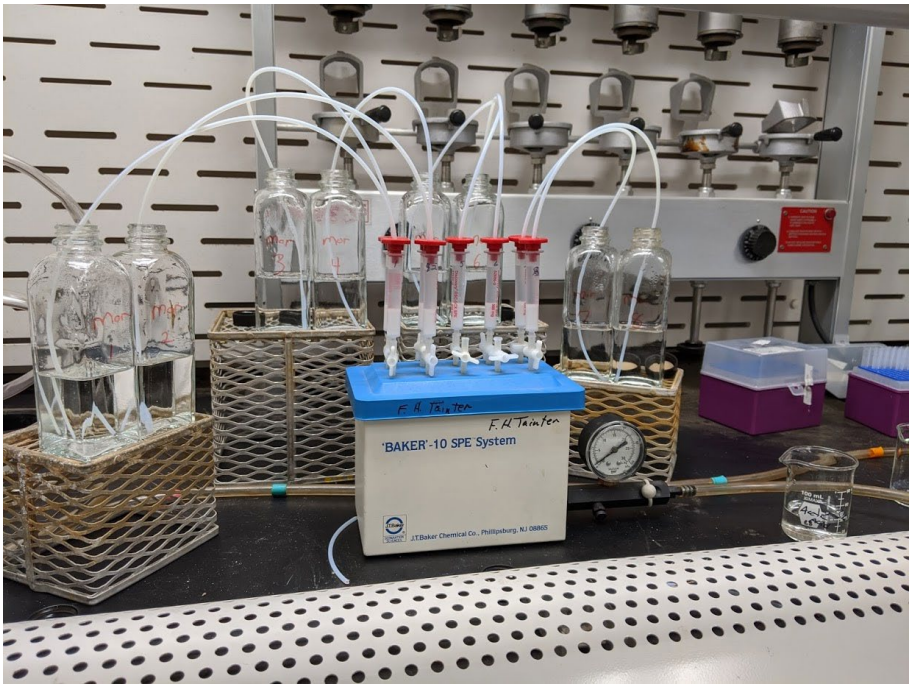



**Figure 3.5.1:** SPE set-up with manifold system

### 3.6 Sample analysis

**Quantification of primary aromatic amines (PAAs) using LC-MS/MS**

UHPLC-MS/MS analysis was performed using an Ultimate 3000 HPLC (Thermo Scientific, Waltham, MA, USA) coupled to an Orbitrap Fusion Tribrid mass spectrometer (Thermo Scientific) equipped with a heated electrospray ion source. Samples were injected onto a Waters (Waters Corp., Milford, MA, USA) Cortecs UPLC T3 (150×2.1 mm, 1.6 μm) column maintained at 32°C. The solvent gradient utilized water containing 0.05% formic acid as mobile phase A, and acetonitrile containing 0.05% formic acid as mobile phase B. The solvent gradient begins with 5% B at 0 minutes, 5% B at 1 minute; 90% B at 10 minutes, 90% B at 12 minutes, a hold at 90% B for 2 minutes, and ends with a 6-minute column re-equilibration at 5% B. The solvent flow rate was constant at 0.15 ml/min and an injection volume of 2 μL was used. The heated electrospray ionization (H-ESI) interface conditions of the mass spectrometer were set at 3500V emitter voltage, 300°C vaporizer temperature, 300 °C ion transfer tube, 55 arbitrary units (arb) of sheath gas, 10 arb of auxiliary gas, and 1 arb sweep gas.

The mass spectrometer was operated in positive ionization mode with parallel reaction monitoring (PRM) MS/MS acquisition for the quantitation of 19 primary aromatic amines. The PRM method was set to include MS2 fragmentation for 19 timed MS/MS ($tMS^2$) scan events targeted for 19 primary aromatic amines **Table 4.2.1**. The targeted $tMS^2$ scan events utilized an Orbitrap resolution of 15,000 at a mass to charge ratio (m/z) of 200, an automatic gain control (AGC) target value of 50,000, and a maximum fill time of 22 ms. The targeted precursor ions were isolated in the quadrupole using a 1.6 m/z unit

isolation window and fragmentation was performed using high-energy C-trap dissociation (HCD) with a collision energy (CE) of 45 eV for all compounds except for 4-Aminoazobenzene which underwent fragmentation using collision-induce dissociation (CID) with a CE of 45 eV. The PRM MS>MS2 transitions used for quantification are provided in **Table 4.2.1.** Quality control checks were performed every 12 samples to ensure the robustness of the method over time [**Table A.1]**

### 3.7 Software

Quantification of primary aromatic amines were performed using Skyline-daily software 64-bit version 19.1.9.350 (MacCoss Lab, Department of Genome Sciences, UW) for small molecule analysis. The total peak area for all reported PRM transitions **(Table 4.2.1)** was used for quantification by means of an external linear calibration curve.

Statistical analysis was conducted via **JMP**® PRO, Version <14>. SAS Institute Inc., Cary, NC, 1989-2019

# 4 RESULTS AND DISCUSSION

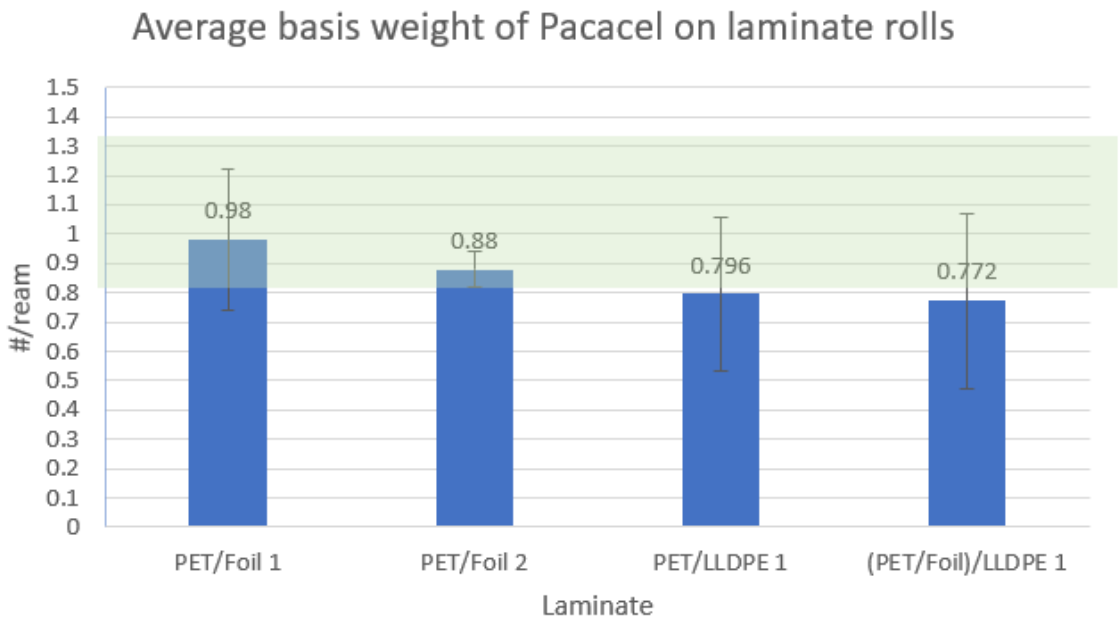



**Fig. 4.1.1:** Average adhesive basis weights for aromatic based adhesive
Numbers indicate usage, where (PET/Foil)/LLDPE 1 was laminated with PET/Foil 1

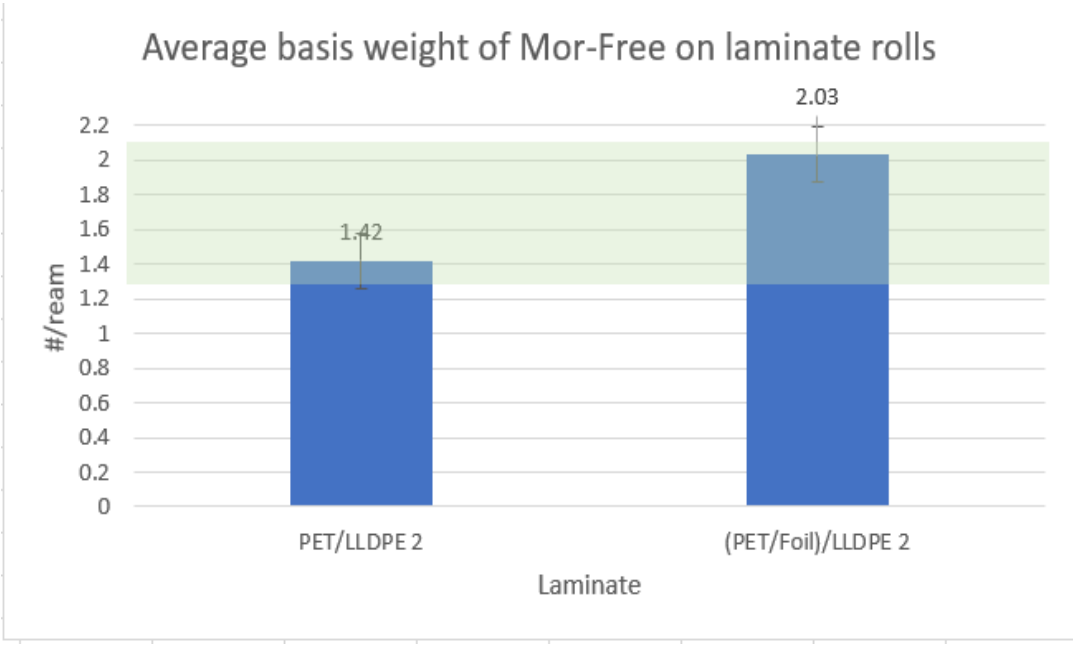



**Fig. 4.1.2:** Average basis weights for aliphatic based adhesive
Numbers indicate usage, where (PET/Foil)/LLDPE 2 was laminated with PET/Foil

## 4.1 Lamination

Four separate rolls of laminated film were successfully produced. After lamination, the rolls were left to cure for the appropriate amount of time listed on the product data sheet of the respective adhesive. The curing allows for a proper and full polymerization of isocyanate and polyol and should theoretically consume all free monomers. As seen in **Figures 4.1.1 & 4.1.2** the target basis weights of the Mor-free aliphatic adhesive fit within manufactures recommendations of 1.3 – 2.1 pounds per ream, but as for the Pacacel aromatic brand two out the four rolls fell just slightly below the recommendation of 0.8 pounds per ream. Due to how close the values were to the recommendation, and the amount of materials needed to run more trials, these were deemed acceptable to continue with laminations.

The rubber transfer roller on the solvent free lamination machine appeared to show signs of a slight warp. This was probably due to the age of the machine or being pressed against another roller for an amount of time, which led to a slightly uneven coating of adhesive and some areas containing wrinkles in the foil. This was overcome by producing a high amount of laminate material to create a large number of pouches. Test pouches were chosen from the stock that were of sufficient quality. This also helped to randomize the selection of pouches from different sections of the roll of laminate.

## 4.2 Analytical Testing

### *4.2.1 Standard curve*

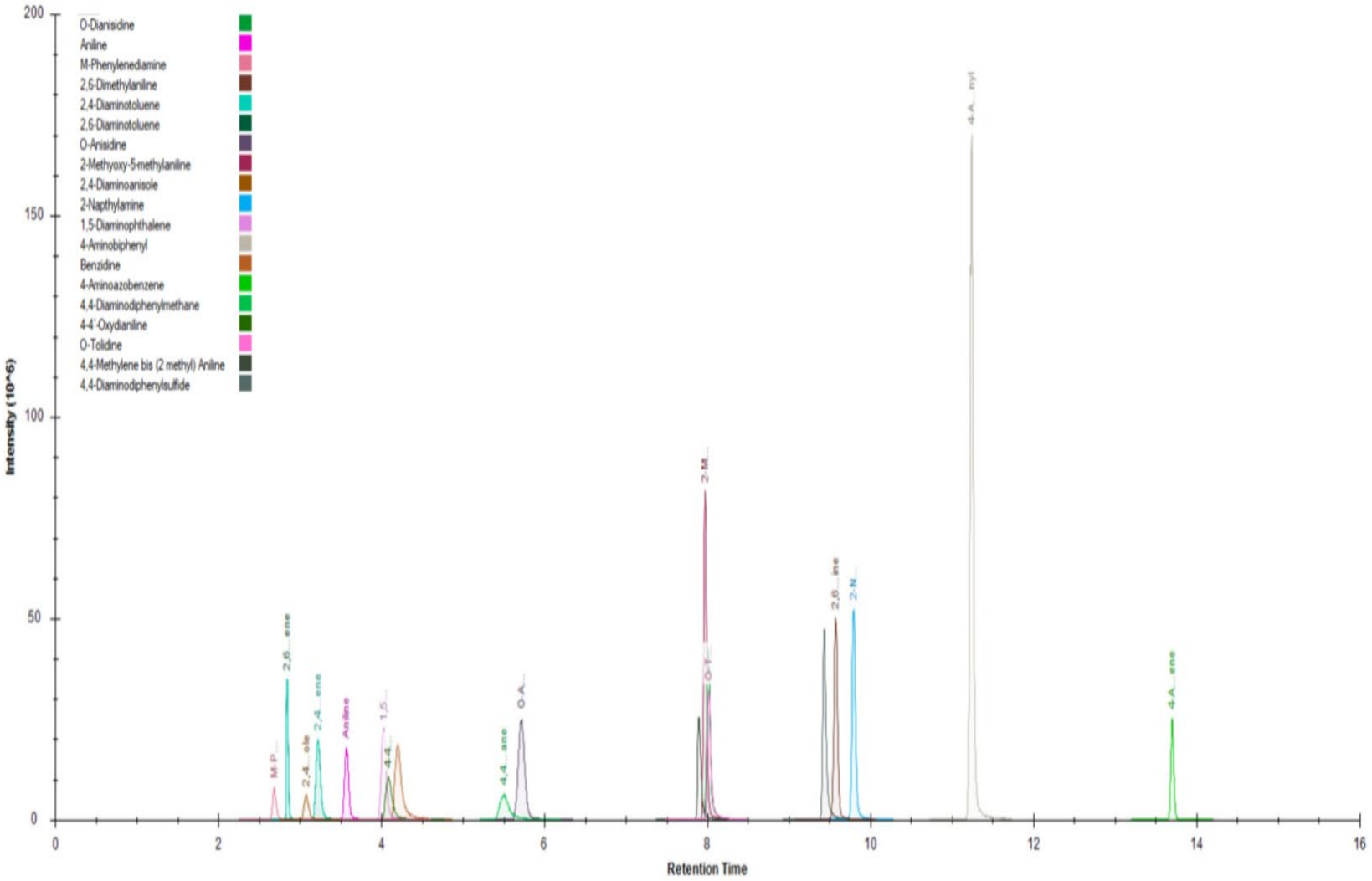
**Figure 4.2.1** Shows the standard curve chromatograph of the 19 PAAs at a concentration of 200ppb. **Figure A.1** shows the percent recovery of the standards which indicates good efficiency for the detection of most compounds.

**Table 4.2.1:** UHPLC-MS/MS PRM standard curve parameters for analysis of PAAs.

| Name | Time start (min) | Time stop (min) | PRM transition | CE (eV) | Instrument LOQ (ppb) |
|---|---|---|---|---|---|
| M-Phenylenediamine | 2.25 | 3.30 | 109.076 > 65.0383, 92.0495, 93.0572, 110.06, 108.0681 | HCD, 45 | 3.1 |
| 2,6′-Diaminotoluene | 2.41 | 3.30 | 123.0917 > 108.0679, 106.0648, 107.0601, 105.0444, 95.0488, 96.0441, 79.0539, 81.057, 80.0492, 67.0414, 77.0383, 91.0415 | HCD, 45 | 3.1 |
| 2,4′-Diaminoanisole | 2.76 | 3.50 | 139.0866 > 108.0678, 107.0602, 124.0629, 123.0551, 95.049, 80.0492, 65.0384 | HCD, 45 | 6.2 |
| 2,4′-Diaminotoluene | 3.00 | 3.55 | 123.0917 > 108.0679, 106.0648, 107.0601, 105.0444, 95.0488, 96.0441, 79.0539, 81.057, 80.0492, 67.0414, 77.0383, 91.0415 | HCD, 45 | 1.5 |
| Aniline | 3.23 | 4.23 | 94.0651 > 95.0489, 105.0445, 51.0227, 50.015, 53.0385, 77.0384, 92.5216, 93.0572 | HCD, 45 | 1.5 |
| 1,5′-Diaminonaphthalene | 3.66 | 4.66 | 159.0917 > 115.0542, 117.0574, 116.0619, 118.0651, 143.0729, 142.0652, 141.0574, 132.0806, 130.0652, 131.0734, 93.057, 96.4179, 99.5334, 158.0841, 157.0766 | HCD, 45 | 3.1 |
| 4.4′-Oxydianiline | 3.78 | 7.20 | 201.1022 > 108.044, 184.0755, 156.0805, 80.0491, 93.0568, 128.062, 129.062, 139.0544 | HCD, 45 | 6.2 |

| | | | | | |
|---|---|---|---|---|---|
| Benzidine | 3.86 | 7.20 | 185.1072 > 167.0731, 168.0805, 184.0996, 166.0654, 141.0698, 169.0647, 115.0542, 93.0571 | HCD, 45 | 6.2 |
| 4,4′-Diaminodiphenylmethane | 5.20 | 7.20 | 199.123 > 106.065, 165.0695, 180.0806 | HCD, 45 | 6.2 |
| O-Anisidine | 5.35 | 6.35 | 124.0757 > 109.052, 108.0438, 80.0493, 92.0493, 65.0384, 81.0568 | HCD, 45 | 1.5 |
| 4,4′-Methylenebis(N,N-dimethylaniline) | 7.37 | 8.00 | 227.1543 > 120.0806, 193.1012, 194.0968, 195.1041, 180.0811, 178.0775 | HCD, 45 | 3.1 |
| 2-Methoxy-5-methylaniline | 7.46 | 8.46 | 138.0913 > 123.0678, 122.0597, 106.0649, 78.0464, 95.0492 | HCD, 45 | 3.1 |
| O-Tolidine | 7.49 | 8.49 | 213.1386 > 196.1122, 197.107, 198.1152, 181.0885, 180.0806, 107.0728, 165.0696, 178.0777 | HCD, 45 | 0.7 |
| O-Dianisidine | 7.49 | 8.49 | 245.1285 > 230.105, 213.1021, 215.0814, 202.1045, 187.0864, 198.0786, 170.0838, 143.0726 | HCD, 45 | 1.5 |
| 4,4′-Diaminodiphenylsulfide | 8.92 | 9.92 | 217.0794 > 124.0212, 199.045, 200.0527, 183.026, 184.0985, 167.0729, 139.0542, 80.0494 | HCD, 45 | 6.2 |
| 2,6′-Dimethylaniline | 9.07 | 10.07 | 122.0964 > 105.0696, 95.0488, 79.0539, 107.0727, 103.0539, 106.0648, 77.0383, 65.0838 | HCD, 45 | 3.1 |
| 2-Naphthylamine | 9.28 | 10.28 | 144.0808 > 127.054, 126.0461, 143.0725, 117.0696, 115.0538, 95.049, 105.0444 | HCD, 45 | 3.1 |
| 4-Aminobiphenyl | 10.73 | 11.73 | 170.0964 > 152.062, 153.0698, 169.0885, 168.0807, 128.0615, 93.0571, 65.0384 | HCD, 45 | 0.39 |
| 4-Aminoazobenzene | 13.20 | 14.20 | 198.1026 > 95.049, 93.057, 92.0492, 77.0382, 105.0444, 125.0468, 118.0648, 110.0602, 153.0698, 152.0618, 169.0886, 170.0965 | CID, 45 | 6.2 |

**Figure 4.2.1:** Chromatograph of standard curve cocktail of 19 PAAs at 200ppb



*4.2.2. System suitability test*

The accuracy, precision, and system suitability of the UHPLC-MS/MS method were examined using a repeatability test of a standard mixture of PAAs using 8 replicates of 2 ul injections at 50 ng/ml. The relative standard deviation of all PAAs were within 5% This is demonstrated in the Appendix **(Table A.2).**

*4.2.3 Linear range & LOQ:*

Examination of a series of standards ranging from 0.048 - 200 ng/ml showed that the instrument method performed well with 2 µL injections below 3.125 ng/ml for most species. This is also seen in the appendix (**Table A.3**).

*4.2.4 Sample analysis via UHPLC MS/MS*:

The resulting analyses of samples via UHPLC-MS/MS compared to the standard curve of 19 PAAs show that the compound aniline was present in quantities above the limit of detection (LOD) in all samples tested. The concentration of aniline in the samples are shown to be significantly different from each other ($p < 0.05$) based on a Tukey statistical analysis - shown in **Figure 4.2.2** where a distinct trend in the clumping of concentrations was seen. Foil as a barrier layer in the laminate was shown to increase migration to the food-contact layer, possibly because all migration occurred only in one direction due to the barrier layer [7].

Low levels of detectable 4-aminobiphenyl was observed in most of the pouches that were laminated with the aliphatic adhesive. In the case of this particular PAA, foil

was not observed to have higher levels of migratable compounds. This contradicts the scenario of aniline. Other compounds were observed above the limit of detection but were not seen in a trend like the two PAAs described earlier. **Table 4.2.4** shows the list of compounds that were detected above the LOD in single pouches that did not show any trend in any one sample variable. **Table 4.2.5** show all the other compounds tested that were not detected above the LOD in any sample. The full sample analysis table is shown in appendix A **[Table A.3].** Benzidine, 4,4-diaminodiphenylmethane, and 4-4'-Oxydianiline did not produce a reproducible signal in the sample matrix and hence are not reported.

**Table 4.2.2**. Samples are expressed as shorthand - defined below:

| | |
|---|---|
| BOPET/Aliphatic/LLDPE - ALI | BOPET/Aromatic/LLDPE - ARO |
| Foil added – ALI-F | Foil added – ARO-F |

**Table 4.2.3:** Average concentration of compounds detected above their limit of detection in all samples (ng/ml)/(ppb)

| | Aniline | 4-Aminobiphenyl |
|---|---|---|
| *B | 0 | 0 |
| ARO | 10.02 ± 0.56 [c] | <LOD |
| ARO-F | 26.63 ± 2.62 [a] | <LOD |
| ALI | 6.37 ± 0.79 [d] | 1.15 ± 0.33 [a] |
| ALI-F | 15.53 ± 1.98 [b] | 0.68 ± 0.07 [b] |

*P < 0.05* *B = Blank

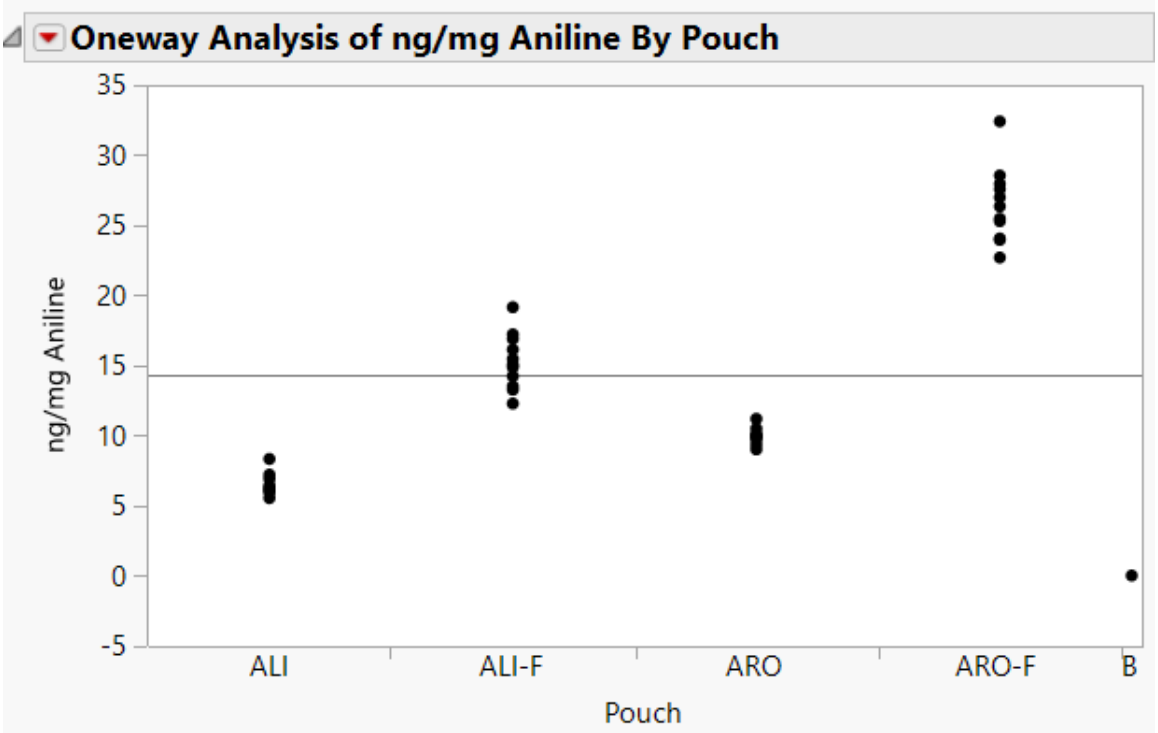



**Figure 4.2.2:** One-way analysis of ng/mg (ppb) Aniline by pouch

**Table 4.2.4** Concentration of compounds observed above their detectable limit in single pouches (ng/ml) (ppb)

| | ARO | ARO-F | ALI | ALI-F |
|---|---|---|---|---|
| O-Dianisidine | 27.02 | | | |
| 2,4-Diaminoanisole | 108.96 | | | |
| 1,5-Diaminonaphthalene | 3.45<br>6.14 | | | |
| 4-Aminobiphenyl | 0.44 | | | |
| 4,4-Methylene bis (2 methyl) Aniline | | 6.83<br>27.09 | | |
| 4,4-Diaminodiphenylsulfide | | | 7.44 | |

**Table 4.2.5** Compounds not detected above their limit of detection in any sample

| | | |
|---|---|---|
| M-Phenylenediamine | 2,6-Diaminotoluene | 2-Napthylamine |
| 2,6-Dimethylaniline | O-Anisidine | 4-Aminoazobenzene |
| 2,4-Diaminotoluene | 2-Methyoxy-5-methylaniline | O-Tolidine |

### 4.3 Discussion

In this study, aliphatic and aromatic isocyanates in polyurethane adhesives were tested for migration of PAAs in laminate structures. The results show that aromatic compounds were found in pouches made with an adhesive that by design has no aromatic precursors. Steps were made in processing of laminations to ensure little to no contamination between samples occurred. The aliphatic adhesive was run on the machine prior to running the aromatic adhesive. Thorough cleaning of rollers was conducted with ethyl acetate before, between, and after runs.

**Possible explanations of why aromatics were detected:**

- Leaching of compounds from the rubber rollers on the machines.

It is possible that previous runs of aromatic based adhesives used on the machine from before this research started may have leached trace amounts of monomers onto the rubber transfer rollers and mixed with the aliphatic adhesive during laminations. This is not likely due to consistent and thorough cleaning with ethyl acetate. Observations of UHPLC-MS/MS results show nearly all pouches that had aromatic adhesives had values of 4-aminobiphenyl below the LOD where only the aliphatic adhesive showed trends of that PAA, making contamination not a viable or logical explanation.

- Trace amounts under normal detectable limits of aromatic compounds in the aliphatic adhesive or LLDPE.

It may be reasonable to hypothesize that contamination may have occurred outside of the lamination processing, but during the converting process. LLDPE as a monolayer pouch

was not tested. That film may have contributed to the aromatic compounds being detected, but as it was not consistent through all the pouches, this seems unlikely. The aliphatic adhesive having inherent low levels below normal detection limits may be a reasonable explanation, but further testing into the adhesive may need to be conducted for that assumption to be made.

- Aliphatic trimerization and breakdown

It is possible for aliphatic compounds to trimerize and form aromatic compounds [8]. Conditions for this process to occur may only have been present during the conditioning of the formed and sealed pouches in which theoretically all free monomers have been polymerized. The compounds observed via UHPLC-MS/MS were low molecular weight, so the trimerized compounds would need to have further breakdown, and while this is not impossible the environment for this pathway to occur makes this solution improbable.

- Shortcomings in method validation

In the initial phase of method validation during the testing of the method recovery, the percent recovery of aniline was seen to be 156% [**Figure A.1**]. A possible reason is that the cocktail may have been spiked with more aniline than intended. Another could be that chemical reactions could have occurred in the cocktail to create more aniline, which may describe why some compounds were below the standard range for acceptable recovery. Either way, this shows that this method may have an affinity to overestimate the amount of aniline in the samples. A review and possibly another round of validation for the method may have to be conducted to erase all doubt and re-run the data with the new models.

The findings from this research further expand upon the research conducted by Aznar et al. This research also proves the migration of PAAs with the use of polyurethane adhesives. Making the laminated material and pouches to be used in this study provided for more control of unknown variables compared to the studies where outsourced laminated materials were used. Though it was shown that aluminum foil used in the lamination had increased levels of migratable aniline, it cannot be concluded that foil directly increases migration in all samples for all compounds since that trend was not seen for 4-aminobiphenyl.

Compared to the study conducted by Pezo et al. where many (18) different laminate structures were tested and at different conditions for each, this thesis focused on the specific structure of BOPET and LLDPE with foil as a barrier. Many of the same specific PAAs were tested in both experiments but The LODs in Pezo's testing were much lower, and thus had a higher sensitivity to detect compounds in their samples. While they were able to see more hits of detectable compounds in the samples they tested, they claim that no samples tested hit above the combined concentration threshold of 10ppb limit in regard to the EU regulation. Pezo et al. also tested a PET/Foil/PE laminate, but did not disclose any specifications regarding the films used or on type of PU adhesive. This thesis also used more rigorous migration test conditions (60°C for 10 days) and tested only the sealant layer, while Pezo immersed squares of laminate at 70°C for 2 hours for the PET/Foil/PE sample. This "worst case" scenario testing may be a reason why this thesis observed migratable PAAs above the 10ppb limit while Pezo did not [9].

Comparatively, Aznar et al. only tested two structures: a metallized PET to a polyethylene film, and a biaxially oriented polypropylene (BOPP) to another BOPP, all laminated with a PU adhesive. Also, the paper was equally ambiguous regarding the specifics on the films and adhesives. The samples were tested "just after manufacturing" which may lead to questions on if the curing process of the films were compliant to manufacturers specifications. Conditioning for the migration test was the same as the Pezo method, with a square piece of laminate being immersed in the food simulant at 70°C for two hours. Again, meaning both the outside and inner-most layer were being tested for extractables. The metallized PET/PE laminate that was tested did find migratable PAAs over the 10ppb limit, with a total concentration converted to aniline equivalents of 26ppb. This thesis found an average aniline concentration of 26.63±2.62ppb in the BOPET/Foil/LLDPE pouches, which would match similar results with the Aznar findings [1]. Though the specific testing conditions were different, the analytical methodology was similar, and the results of the similar pouch structures showed correlative results. The other laminate structure Aznar tested was found to be under the 10ppb regulation threshold. The former laminate's results were attributed to polyethylene's low barrier to small molecular weight compounds.

# 5 CONCLUSION

Four separate rolls of laminate films were produced, made into pouches, and then tested for migration of primary aromatic amines. Two rolls were BOPET/LLDPE laminates, one utilizing an aromatic PU adhesive, and one with an aliphatic adhesive. The other two rolls were BOPET/Foil/LLDPE laminates with the same adhesive differences. A standard curve of 19 PAAs was made and was compared against extracts from the pouch samples of the aforementioned four laminate films. Based on the results, on average ($p<0.05$), the pouches that were tested containing aromatic based polyurethane (PU) adhesive, and pouches with aliphatic based PU adhesive with foil, exceeded the EU regulatory standard detection limit of PAAs being present at $10ng/g^{-1}$ (ppb) of food. The compound aniline was found in all pouches tested, and it was found that foil in the laminate showed an increase in migration to the food contact layer compared to pouches without foil. It is worth mentioning that since this was a targeted analysis of 19 PAAs and the regulation mentions “All migratable PAAs” [6], this may not be a sufficient method suitable for industry. However, with the quality of results and significance of finding aromatic compounds in an aliphatic based laminate system, this method would be satisfactory for use in a quality control setting. Aromatic compounds found in pouches that used aliphatic adhesives were not expected, and further research may need to be conducted to ensure that it was not a contamination issue.

## 5.1 Future Works

Steps have been initialized for a migration test of a mono layer LLDPE pouch. If any detected contaminates came specifically from the sealant layer, and not from the migration from the adhesive, this test should allow for that possibility to be detected. The same procedure will be followed with the same LLDPE that was used for laminations. 10 X 10 $cm^2$ inside layer pouch with 100 mL of pure water containing 3% acetic acid will be sealed and conditioned at 60°C for 10 days. The same SPE method will be utilized, and the same analytical equipment will be used for measurements.

After testing the LLDPE, analysis on the aliphatic adhesive used in this study to check for contamination would be conducted. Analysis on the polyol component and the isocyanate component would need to be done separately to check for aromatic compounds that could have reacted to form PAAs.

Other opportunities for further research stemming from this project include running the same tests on the other brands of adhesive from the same manufacturer as the ones used in this research. This could be done to check for patterns in similar detectable compounds (PAAs) that may be detected. Conversely, conducting tests using adhesives from different manufacturers using the same conditions and looking for patterns of detectable compounds (PAAs) specific to the proprietary isocyanate used.

Lastly, looking into the differences in lamination techniques and whether solvent-based, water-based, or solvent-less lamination has a difference on the amount of migratable PAAs detected using the same adhesive.

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## Appendix A: Analytical data

**Figure A.1:** Percent recovery from method blank

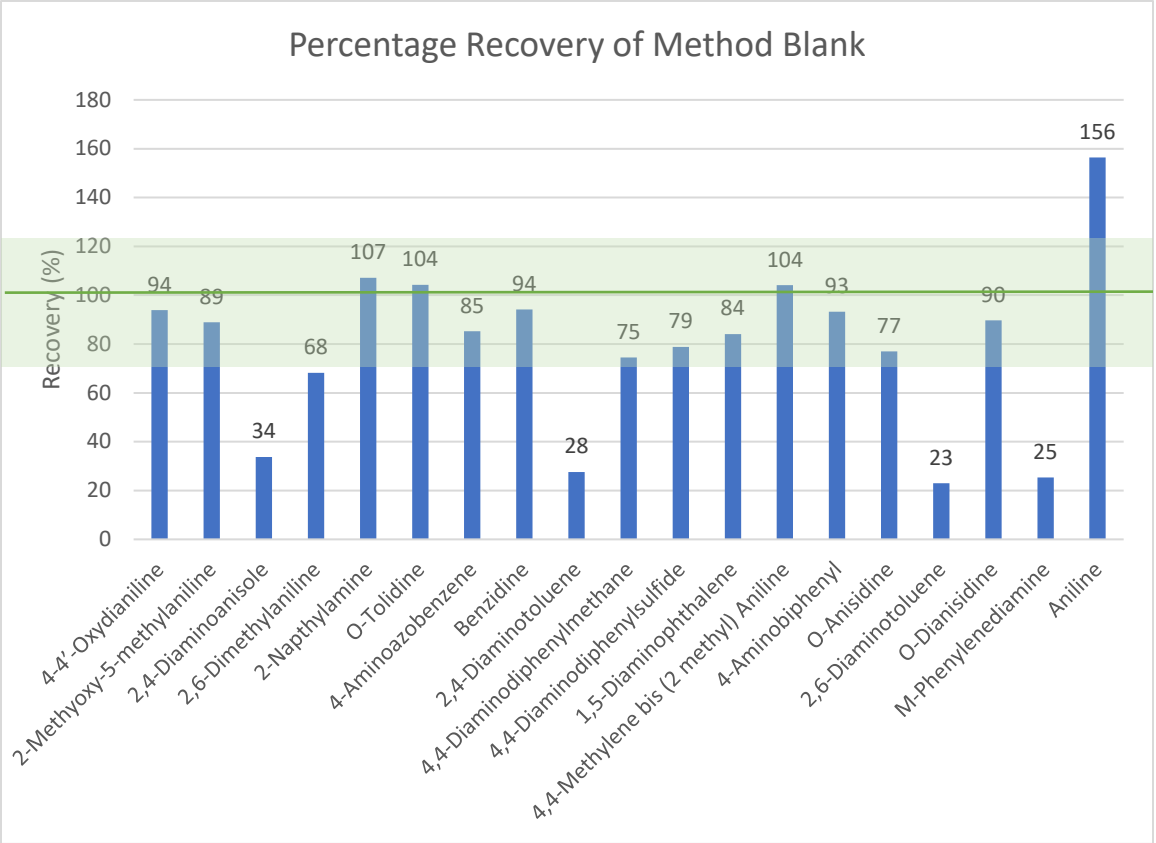

**Table A.1:** System quality control checks**:**
Standard mixture (50 ng/ml) injected at an interval of 12 samples to check for analysis robustness over the duration of the sample analysis.

| **Compound** | **Average Concentration (ng/ml)** | **% RSD** |
|---|---|---|
| O-Dianisidine | 51.69 | 3.94 |
| Aniline | 52.77 | 5.32 |
| M-Phenylenediamine | 54.84 | 5.95 |
| 2,6-Dimethylaniline | 54.88 | 2.86 |
| 2,4-Diaminotoluene | 45.56 | 12.26 |
| 2,6-Diaminotoluene | 54.31 | 4.34 |
| O-Anisidine | 55.77 | 3.57 |
| 2-Methyoxy-5-methylaniline | 55.31 | 3.19 |
| 2,4-Diaminoanisole | 48.20 | 4.59 |
| 2-Napthylamine | 54.29 | 2.41 |
| 1,5-Diaminonaphthalene | 50.44 | 4.24 |
| 4-Aminobiphenyl | 51.15 | 3.62 |
| 4-Aminoazobenzene | 50.06 | 4.71 |
| O-Tolidine | 54.28 | 3.88 |
| 4,4-Methylene bis (2 methyl) Aniline | 50.38 | 4.73 |
| 4,4-Diaminodiphenylsulfide | 59.58 | 3.75 |

**Table A.2**. System suitability (SST):

The accuracy and precision of the LC-MS/MS method and the system suitability was examined using a repeatability test of a standard mixture of PAAs using 8 replicates of 2 ul injections at 50 ng/ml. The relative standard deviation of all PAAs were within 5%. Conclusion: The method and the system passed the suitability test based on the values provided below.

| | Concentration (ng/ml) | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Replicate Name | O-Dianisidine | Aniline | M-Phenylene | 2,6-Dimethylan | 2,4-Diaminoto | 2,6-Diaminotol | O-Anisidine | 2-Methyoxy- | 2,4-Diaminoa | 2-Napthylami | 1,5-Diaminon | 4-Aminobiph | Benzidine | 4-Aminoazob | 4,4-Diaminod | 4-4'-Oxydiani | O-Tolidine | 4,4-Methylene | 4,4-Diaminoc |
| PAA_50ppb_SST_1 | 50.01 | 50.67 | 49.10 | 51.13 | 45.96 | 52.33 | 52.44 | 52.40 | 47.62 | 51.03 | 49.64 | 46.92 | 50.89 | 46.90 | 47.47 | 48.82 | 48.73 | 49.55 | 53.08 |
| PAA_50ppb_SST_2 | 51.58 | 50.61 | 48.90 | 52.90 | 41.40 | 51.50 | 52.34 | 52.57 | 50.66 | 51.84 | 52.02 | 46.44 | 52.61 | 48.08 | 49.34 | 51.92 | 50.85 | 52.31 | 54.60 |
| PAA_50ppb_SST_3 | 51.78 | 52.09 | 49.45 | 52.03 | 45.26 | 53.90 | 55.05 | 53.71 | 50.03 | 51.57 | 50.98 | 47.57 | 51.78 | 47.78 | 49.82 | 51.18 | 50.40 | 53.29 | 53.62 |
| PAA_50ppb_SST_4 | 52.17 | 50.71 | 48.76 | 52.48 | 47.42 | 52.78 | 52.77 | 53.84 | 51.30 | 52.80 | 51.88 | 48.06 | 51.99 | 48.42 | 48.97 | 52.82 | 50.83 | 52.88 | 56.03 |
| PAA_50ppb_SST_5 | 52.32 | 51.34 | 51.37 | 52.12 | 46.40 | 54.09 | 53.34 | 53.66 | 50.20 | 52.27 | 51.25 | 48.26 | 52.43 | 48.03 | 50.00 | 50.50 | 52.06 | 52.33 | 55.46 |
| PAA_50ppb_SST_6 | 52.53 | 50.73 | 50.90 | 53.13 | 43.88 | 52.46 | 52.76 | 53.77 | 51.44 | 52.99 | 51.58 | 49.29 | 50.39 | 48.32 | 49.56 | 52.44 | 51.27 | 53.47 | 55.56 |
| PAA_50ppb_SST_7 | 50.62 | 50.95 | 50.47 | 51.79 | 46.39 | 53.30 | 52.72 | 52.71 | 49.81 | 51.18 | 51.42 | 48.00 | 50.86 | 48.82 | 47.08 | 49.71 | 49.27 | 53.29 | 54.69 |
| PAA_50ppb_SST_8 | 51.99 | 52.57 | 50.18 | 53.35 | 43.64 | 55.11 | 55.15 | 54.55 | 51.48 | 53.11 | 52.35 | 49.43 | 53.70 | 50.69 | 49.27 | 53.06 | 52.04 | 53.77 | 54.60 |
| **AVERAGE** | **51.62** | **51.21** | **49.89** | **52.37** | **45.04** | **53.18** | **53.32** | **53.40** | **50.32** | **52.10** | **51.39** | **48.00** | **51.83** | **48.38** | **48.94** | **51.31** | **50.68** | **52.61** | **54.70** |
| **% RSD** | **1.70** | **1.44** | **1.96** | **1.42** | **4.34** | **2.17** | **2.13** | **1.41** | **2.53** | **1.57** | **1.62** | **2.17** | **2.11** | **2.25** | **2.21** | **2.98** | **2.36** | **2.55** | **1.81** |

**Table A.3:** UHPLC-MS/MS sample analysis of all 48 pouches

| | Concentration (ng/ml) | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Replicate Name** | O-Dianisidine | Aniline | M-Phenylened | 2,6-Dimethyla | 2,4-Diaminotc | 2,6-Diaminotc | O-Anisidine | 2-Methyoxy-5 | 2,4-Diaminoanisole | 2-Napthylamir | 1,5-Diaminona | 4-Aminobiphenyl | Benzidine | 4-Aminoazobe | 4,4-Diaminodi | 4-4'-Oxydianil | O-Tolidine | 4,4-Methylene | 4,4-Diaminodi |
| **Instrument Linear Range (ng/ml) LOQ** | 1.56 - 100 | 0.78 - 100 | 3.125 - 100 | 3.125 - 200 | 1.56 - 100 | 3.125 - 100 | 1.56 - 100 | 3.125 - 100 | 6.25 - 200 | 3.125 - 100 | 3.125 - 100 | 0.39 - 100 | 6.25 - 200 | 6.25 - 100 | 6.25 - 100 | 6.25 - 200 | 0.78 - 50 | 3.125 - 100 | 6.25 - 200 |
| **Calibration Curve $R^2$** | 0.9999 | 1 | 0.9989 | 0.9997 | 0.9998 | 0.9989 | 0.9995 | 0.9974 | 0.9998 | 0.9982 | 1 | 0.9993 | 0.9998 | 0.9976 | 0.9995 | 1 | 0.9998 | 0.9998 | 0.999 |
| Blank_1 | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| Blank_2 | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| Blank_3 | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| P-1 | **27.02** | **11.17** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | **108.96** | <LOD | <LOD | **0.44** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| P-2 | <LOD | **10.12** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| P-3 | <LOD | **10.48** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| P-4 | <LOD | **10.09** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | **6.14** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| P-5 | <LOD | **9.97** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| P-6 | <LOD | **9.36** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | **3.45** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| P-7 | <LOD | **9.83** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| P-8 | <LOD | **8.99** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| P-9 | <LOD | **10.09** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| P-10 | <LOD | **10.56** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| P-11 | <LOD | **9.75** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| P-12 | <LOD | **9.88** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| PF-1 | <LOD | **28.52** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
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| PF-3 | <LOD | **27.92** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | **27.09** | <LOD |
| PF-4 | <LOD | **32.38** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| PF-5 | <LOD | **24.03** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| PF-6 | <LOD | **26.32** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| PF-7 | <LOD | **23.93** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| PF-8 | <LOD | **26.96** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| PF-9 | <LOD | **25.45** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| PF-10 | <LOD | **27.54** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| PF-11 | <LOD | **28.54** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| PF-12 | <LOD | **25.26** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | **6.83** | <LOD |
| M-1 | <LOD | **8.31** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | **1.54** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| M-2 | <LOD | **6.09** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | **1.29** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| M-3 | <LOD | **5.93** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | **1.29** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| M-4 | <LOD | **7.20** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | **1.24** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
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| M-11 | <LOD | **5.52** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| M-12 | <LOD | **5.94** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | **0.54** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| B | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
| MF-1 | <LOD | **12.26** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | **0.78** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
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| MF-3 | <LOD | **14.21** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | **0.63** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
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| MF-11 | <LOD | **16.87** | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD | <LOD |
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## Appendix B: Technical data information

### B.1: LLDPE Technical data sheet

| Processing/Physical Characteristics | Value | Unit | Test Standard |
|---|---|---|---|
| **ASTM Data** | | | |
| Melt Flow Index, MFI | 0.85 | g/10min | ASTM D 1238 |
| Temperature | 190 | °C | - |
| Load | 2.16 | kg | - |

| Thermal properties | Value | Unit | Test Standard |
|---|---|---|---|
| **ASTM Data** | | | |
| Vicat Temperature | 130 | °C | ASTM D 1525 |
| **Other Standards[S]** | | | |
| Melting Temperature | 134 | °C | Dow Method |

S: These properties are reported by the producer according standards that are different to our defaults.

| Optical properties | Value | Unit | Test Standard |
|---|---|---|---|
| **ASTM Data** | | | |
| Gloss | 14 | - | ASTM D 2457 |
| Haze | 42 | % | ASTM D 1003 |

| Other properties | Value | Unit | Test Standard |
|---|---|---|---|
| Density | 962 | kg/m³ | ASTM D 792 |

| Film Properties | Value | Unit | Test Standard |
|---|---|---|---|
| **ASTM Data** | | | |
| Tensile Strength at Yield, MD | 28.3 | MPa | ASTM D 882 |
| Tensile Strength at Yield, TD | 30.3 | MPa | ASTM D 882 |
| Tensile Strength at Break, MD | 37.2 | MPa | ASTM D 882 |
| Tensile Strength at Break, TD | 34.1 | MPa | ASTM D 882 |
| Elongation at Break, MD | 500 | % | ASTM D 882 |
| Elongation at Break, TD | 600 | % | ASTM D 882 |
| Type of extrusion | blown | - | - |
| Thickness of specimen | 0.025 | mm | - |

## B.2 BOPET Technical data sheet

MITSUBISHI POLYESTER FILM

# 24CTN Packaging Film

PRODUCT BULLETIN

### Description

Hostaphan® 24CTN is a corona treated polyester film that combines high strength and durability, good dimensional stability and excellent chemical resistance. This product is corona treated on one side to enhance wettability.

### Performance

Hostaphan® 24CTN film has excellent slip and good dimensional stability over a wide temperature range. It can be *coated* or *metallized* to enhance barrier properties. This film can be used in a variety of printing and converting processes and packaging applications.

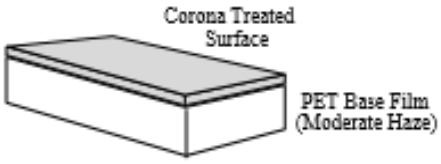
### FDA Status

Both sides of Hostaphan® 24CTN can be used for direct food contact applications subject to limitations found in 21 CFR 177.1630 and in accordance with good manufacturing practices. Contact your Mitsubishi Polyester Film Sales Representative for more information.

### Benefits

- Corona treatment provides surface wettability of 52 dynes or greater
- Can be coated or printed using methods suitable for corona treated polyester
- Can be coated or printed using methods suitable for plain polyester
- Excellent handling characteristics

### Schematic of Hostaphan® 24CTN



## Typical Properties of Hostaphan® 24CTN Film

The Hostaphan® 24CTN property values below are typical measurements. Further guidance on series selection, functional behavior by end use, film processing, standard roll configuration and gauges is available through a Mitsubishi Polyester Film Sales Representative.

| Property | | Unit of Measure | Typical Value* | Test Method |
|---|---|---|---|---|
| Area Yield | | in²•mil/lb<br>m²•mm/kg | 19,800<br>717 | ASTM D 4321 |
| Tensile Strength | MD | psi<br>kg/cm² | 32,000<br>2,250 | ASTM D 882 |
| Yield Strength (F5) | MD | psi<br>kg/cm² | 15,000<br>1,050 | ASTM D 882 |
| Ultimate Elongation | MD | % | 100 | ASTM D 882 |
| Modulus | MD | psi<br>kg/cm² | 600,000<br>42,200 | ASTM D 882 |
| Coefficient of Friction A/B | Static<br>Kinetic | -- | 0.40<br>0.37 | ASTM D 1894 |
| Shrinkage | MD<br>TD | % | 1.5<br>0.4 | 30 min. at 150°C |
| Surface Tension (corona treated side) | | dynes | 52 minimum | ASTM D 2578 |
| Tear Strength | MD | g/mil<br>g/µm | 20<br>0.8 | ASTM D 1922 |
| Moisture Vapor Transmission Rate | | g /100 in²•24 hr<br>g /m²•24 hr | 3.7 (48 ga.) 1.9 (92 ga.)<br>57 (48 ga.) 29 (92 ga.) | ASTM E 96 |
| Oxygen Transmission Rate | | cc /100 in²•24 hr•atm<br>cc /m²•24hr•atm | 9.1 (48 ga.) 4.6 (92 ga.)<br>141 (48 ga.) 70 (92 ga.) | ASTM D 3985 |
| Density | | g/cm³ | 1.3975 | ASTM D 1505 |
| Total Haze* | | % | 2.7 (48 ga.)<br>3.8 (92 ga.)<br>4.6 (118 ga.) | ASTM D-1003 |

* Values for reference data only. Contact a Mitsubishi Polyester Film Sales Representative for actual gauges available.
Approved: AP 3/2019

Mitsubishi Polyester Film, Inc.• 2001 Hood Road • P.O. Box 1400 • Greer S.C. 29652 • 864-879-5000 • www.mpefilm.com

## B.3 Aliphatic adhesive technical data sheet

**Technical Information**

# MOR-FREE™ 1390A/ MOR-FREE™ C-33

**Description**

MOR-FREE™ 1390A/ MOR-FREE™ C-33 is a two component, aliphatic solventless polyurethane adhesive system which is applied at low temperature. This adhesive system is used in film to film laminations including film to film retort applications and where non-yellowing of the lamination is desired. This adhesive system provides high heat and chemical resistance. This adhesive system is patented , U.S. Patent Number 5,731,090.

Avoid hot room cure for the first 48 hours.

**Typical Applications**

Applications where higher temperature resistance is required.
Films should be printed with suitable ink for lamination.
For food packaging, medical packaging and industrial applications.
Hot fill applications.
Lamination of PETP, PA, PP, PE (including EVA-types) structures.
Non-foil condiment laminations.
Retort laminations.

**Suggested Substrates**

Not recommended for laminating aluminium foil.
Oriented polyamide film (OPA) or oriented nylon (BON).
Polyester (PET).
Reverse printed or unprinted substrates.
Treated polyethylene PE (including EVA-types).
Treated polypropylene (PP), (minimum 38 dyne/cm).

| Typical Physical Properties | Adhesive | Coreactant | Unit |
|---|---|---|---|
| Component Type | OH | NCO | |
| Solids Content | 100 | 100 | % |
| Viscosity (25°C) | 3700 | 1800 to 4000 | mPa·s |
| Weight/Gallon | 9.85 | 9.75 | lb |
| Mix Ratio by Weight (PBW) | 100 | 100 | |
| Mix Ratio by Volume (PBV) | 100 | 100 | |
| Wet Appearance | • Clear to Hazy<br>• Colourless to Slightly Yellow<br>• Liquid | • Colourless to Slightly Yellow<br>• Liquid | |

**Recommended Processing Guidelines**

This system has to be used with a laminating machine designed for solventless lamination, equipped with a suitable adhesive application unit and a tension control system suitable for winding laminated films with low initial tack.
For trial runs it is recommended to prepare no more adhesive than can be used within 15-30 minutes. The mixing of the two components must be done in such way as to obtain a homogeneous mix.
For regular production, it is indispensable to use a mixing and dosing device or pump, which continuously mixes the adhesive in the chosen mix ratio, controls the feeding to the application unit, and stops automatically in case of machine standstills.
When processing the adhesive, the precautionary measures applying to working with isocyanates have to be observed.
It is recommended to preheat the adhesive to a temperature of 43 to 54°C in order to take it out of the containers.

**General Comments**

Dow's Technical Service is ready to supply assistance in regards to the correct use of our products.
Interaction may occur with other components of the structure. Inks, retained solvents from any source, substrates, additives, coatings and the packed product are some of the components that may cause a property change of the total structure.
Before regular production, the end user is responsible to verify the suitability and performance properties of the total construction for the intended end use application, including the suitability of the process, construction and components.
If used in conjunction with high slip films (COF <0.2), it is strongly recommended to verify that potential film property changes, due to the lamination process and materials, are acceptable for the end use performance requirements.
The Coreactant or Catalyst must be used at the recommended mix ratio to achieve the desired properties.
This product is sensitive to moisture and should be stored under and transferred with dry nitrogen.

**Recommended Application Weight**

Apply 1.3 to 2.1 g/m² dry, depending on substrate, printing and application.



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**Nip Temperature**

For a good lamination adhesion bonds, nip temperature should be 49 to 71°C.

The rubber roll in the nip with hardness of 85 Shore A or greater is recommended.

**Slitting / Rewind Time**

Slitting and rewind is possible after 5.0 to 7.0 day at 25°C (77°F).

**Curing Time**

Converters should verify appropriate cure times and conditions for their individual application.

For best results, a post lamination curing temperature of 45°C (113°F) is recommended.

Full cure and maximum chemical and thermal properties develop within 10.0 to 14.0 day at 21°C (70°F). Post curing at elevated temperatures can reduce this time.

It is necessary to wait until complete curing has taken place before the laminate is fit for use.

| Suggested Application and Operating Guidelines | Adhesive | Unit |
|---|---|---|
| Application Temperature | 43 to 54 | °C |

**Suggested Cleanup Guidelines**

A proper cleaning procedure should be implemented and practiced as part of the machine operation.

If the machine is stopped for more than 30 minutes, the mixing device and the application rolls should be cleaned before the adhesive becomes insoluble due to progressive curing.

Ethyl acetate is a suitable solvent for cleaning. Other solvents such as MEK or Acetone may also be used.

If the adhesive has become cured on the application rolls, a suitable chemical cleaner may need to be used to remove the residue.

**Storage and Shelf Life Guidelines**

The expiry date of each product is the date reported on the label of the package.

The product may be stored up to stated expiry date provided that the product is stored in a dry and cool, well ventilated place between 5 - 35°C (41 - 95°F) unopened in the original shipping container.

Opened containers should be used as quickly as possible.

Opened shipping containers, especially those of NCO-containing products, should be fitted with desiccant drier tubes to minimize moisture contamination.

**FDA and/or European Food Contact Compliance**

Due to the evolving nature of European and FDA food contact compliances, please contact Dow's Customer Information Group for the most up to date food contact compliance information. Call 800-258-2436 or use the web form at Dow.com for complete FDA and European food contact statements available.

**Notes**

These are typical properties only and are not to be construed as specifications. Users should confirm results by their own tests.

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c. use as a critical component in medical devices that support or sustain human life; or
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## Additional Information

| | | | |
|---|---|---|---|
| **North America** | | **Europe/Middle East** | +800-3694-6367 |
| U.S. & Canada: | 1-800-441-4369 | | +31-11567-2626 |
| | 1-989-832-1426 | Italy: | +800-783-825 |
| Mexico: | +1-800-441-4369 | | |
| **Latin America** | | **South Africa** | +800-99-5078 |
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| Brazil: | +55-11-5188-9000 | | |
| Colombia: | +57-1-219-6000 | **Asia Pacific** | +800-7776-7776 |
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## B.4 Aromatic adhesive technical data sheet:

TDS

**DOW PACACEL L75-191**

### Product Overview

Pacacel solventless adhesive is used in applications ranging from general performance to high performance. This product provides high run speeds, fast cure time, and excellent appearance. Pacacel is designed for laminating combinations of PE, PET, OPP, Metallized films, Foil, Alox, Cellophane, CPP, and Nylon.

### Product Specifications

Application Method: Smooth roll transfer Coreactant: CR 85, CR 89, or CR 88-141
Coating Weight: .8-1.3 ppr
Carrier: Solvent-Free
Chemistry: Polyester Urethane
Color: Colorless to Light Yellow Liquid
Density: 9.39 Lbs/gallon
Mix Ratio: CR 85 100:50, CR 89 100:60 Key Applied Solids: 100%
Supplied Solids: 100%
Cure Time 4-8 hr slit
Mixed Viscosity 2300 cps at RT
Nip Temperature 120-150 F
Substrates: PE, Pet, OPP, Metalized films, foil, Alox, cellophane ,CPP, NYLON
Bond Strength 900-1500 gli Viscosity 3,000 cPs @ 25 °C
**Primary Chemistry:** Polyester Urethane

### Features & Benefits

*Fast cure speed with 4-8 hour time to slit
*Broad FDA and EU compliance
*Fast run speeds with excellent appearance

### Applications

Stand-Up Pouches, Bottle Labels, Coffee bags, Hot Fill Pouches, Meat and Cheese Packaging, Snack Food Packaging, General Industrial

### Features & Benefits

L75-191 features broad FDA and EU compliance after 2-day cure time, 4-8 hour time to slit, high run speeds without misting and improved appearance on METPET, METOPP to heavy white ink backgrounds at high speeds.

### Product Details

**Key Properties**

Application Method : Smooth roll transfer
Coreactant : CR 85, CR 89, CR 88-141
Coating Weight : .8-1.3 ppr
Carrier : solvent free
Chemistry : Polyester Urethane
Color : Colorless to Light Yellow Liquid
Density : 9.39 Lbs/gallon
Mix Ratio :CR 85 100:50 / CR 89 100:60 / CR 88-141 100:65
Recommended Diluent : NA
Drying Web Temperature : NA
Key Performance Benefits : Fast cure speed, fast run speed with excellent appearance, broad
FDA Shelf Life : 365 days
Applied Solids : 100 %
Supplied Solids :100 %
Solvent : none
Thinner : NA
Cure Time : 4-8 hr slit
Mixed Viscosity : 2300 cps at RT
Nip Temperature : 120-150 F
Nominal Application Temperature : 90-100 F
Post Process Time : 2 Day full FDA
Pot Life : 30 minutes at 100 F
Substrates : PE, Pet, OPP, Metalized films, foil, Alox, cellophane ,CPP, NYLON
Bond Strength : 900-1500 gli
Viscosity : 3,000 cPs @ 25 °C

## Appendix C: List of abbreviations

**Table C.1** List of abbreviations

| List of abbreviations | |
|---|---|
| PU | Polyurethane |
| BOPET | Biaxially oriented polyethylene terephthalate |
| PET | Polyethylene terephthalate |
| LLDPE | Linear low-density polyethylene |
| LDPE | Low density polyethylene |
| HDPE | High density polyethylene |
| PAA | Primary aromatic amine |
| NIAS | Non-intentionally added substance |
| SPE | Solid phase extraction |
| UHPLC | Ultra-high-performance liquid chromatography |
| MS/MS | Tandem mass spectrometry |
| *m/z* | Mass-to-charge ratio |
| CE | Collision energy |
| FCM | Food contact material |
| FCS | Food contact surface |
| FCA | Food contact article |
| EU | European Union |
| GC | Gas chromatography |
| PRM | Parallel reaction monitoring |
| MRM | Multiple reaction monitoring |
| HES-I | Heated electrospray ionization |
| CFR | Code of Federal Regulation |
| FDA | Food and Drug Administration |
| AGC | Automatic gain control |
| HCD | High collision dissociation |
| CID | Collision induced dissociation |
| LOD | Limit of detection |
| LOQ | limit of quantitation |