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INVESTIGATION OF THE EFFECTS OF BISPHENOL A AND NONYLPHENOL ON THE TRANSCRIPTIONAL PROFILES OF *SACCHAROMYCES CEREVISIAE* GENOME

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ÖZET

BİSFENOL A VE NONİLFENOL'ÜN *SACCHAROMYCES CEREVISIAE* GENOMU TRANSKRİPSİYON PROFİLLERİ ÜZERİNE ETKİLERİNİN ARAŞTIRILMASI

Bisfenol A (BPA) ve nonilfenol (NP) iyi bilinen endokrin bozucu kimysallar olup çeşitli endüstriyel ürünlerin üretiminde yapıtaşı olarak kullanılmakta ve sürekli çevreye salınmaktadırlar. BPA ve NP maruziyeti altındaki ökaryotik hücre genomunun yeniden programlamasını tespit etmek için *Saccharomyces cerevisiae* model organizma olarak kullanıp *S. cerevisiae* BY4742 suşunun düşük (50 mg/L BPA; 1 mg/L NP) ve yüksek (300 mg/L BPA; 5 mg/L NP) konsantrasyonlardaki BPA ve NP'ye karşı genom ölçekli transkripsiyon profilleri analiz edildi. 50 mg/L BPA'ya 180 dk maruziyette 81 gen baskılanırken 104 genin aktivitesi artmıştır. Aynı zamanda 300 mg/L BPA maruziyetinde, 378 gen baskılanırken 606 genin aktivitesi anlamlı bir şekilde artmıştır. Diğer taraftan, 1 mg/L NP'ye 120 dk maruz kalan maya hücrelerinde 187 genin (63 baskılanmış ve 124 indüklenmiş) ekspresyon seviyesi değişirken 180 dk maruziyette 103 genin (56 baskılanmış ve 47 indüklenmiş) ekspresyon seviyesi değişmiştir. Aynı zamanda 5 mg/L NP'ye 120 dk maruziyette 678 genin (168 baskılanmış ve 510 indüklenmiş) ekspresyonu değişmiş olup 180 dk maruziyette 688 genin (215 baskılanmış ve 473 indüklenmiş) ekspresyon seviyesi değişmiştir. BPA ve NP'nin farklı konsantrasyonlarında benzer prosesler etkilenmesine rağmen ekpresyon seviyesi değişmiş genlerin sayısı ve etkilenme derecesi düşük ve yüksek konsantrasyonlarda belirgin bir şekilde farklılık göstermiştir. 300 mg/L BPA maruziyetinde oksidatif fosforilasyon, trikarboksilik asit döngüsü, ribosomal aktivite, replikasyon ve kimyasala cevap ile ilişkili genlerin ekspresyon seviyeleri belirgin bir şekilde değişmiştir. Ayrıca 5 mg/L NP maruziyetinde de oksidatif fosforilasyon, hücre duvarı biyogenezi, ribosomal biyogenez, RNA işlenmesi, ısı şok proteinleri ve ubiquitin-konjugasyon enzimleri ile ilişkili genlerin ekspresyon seviyesi ciddi bir şekilde değişmiştir. Ancak BPA ve NP'nin düşük konsantrasyonlarında etkilenen genlerin ekspresyon seviyeleri hafif değişiklikler göstermiştir. Bu sonuçlar maya hücrelerinin BPA ve NP'ye transkripsiyon seviyesindeki tepkilerinin konsantrasyona bağlı olarak farklı genler üstünden gerçekleştiğini göstermiş ve BPA ile NP'nin etki mekanizmalarının altında yatan moleküler mekanizmalar hakkında önemli bilgiler sağlamıştır.

Anahtar sözcükler: Bisfenol A, nonilfenol, transkripsiyon profilleri, *Saccharomyces cerevisiae*, maruziyet

ABSTRACT

INVESTIGATION OF THE EFFECTS OF BISPHENOL A AND NONYLPHENOL ON THE TRANSCRIPTIONAL PROFILES OF *SACCHAROMYCES CEREVISIAE* GENOME

Bisphenol A (BPA) and nonylphenol (NP), well-known endocrine disrupting chemicals, are used as building-blocks of various industrial products and continuously leach into the environment. To capture the genome reprogramming in eukaryotic cells under BPA and NP exposure, *Saccharomyces cerevisiae* was used as model organism and the genome-wide transcriptional profiles of *S. cerevisiae* BY4742 strain were analyzed in response to low (50 mg/L BPA; 1 mg/L NP) and high inhibition (300 mg/L BPA; 5 mg/L NP) concentrations of BPA and NP. 81 genes were downregulated and 104 genes were upregulated in response to 50 mg/L BPA for 180 min. Meanwhile, 378 genes were downregulated and 606 genes were significantly upregulated upon exposure to 300 mg/L BPA. On the other hand, 187 genes (63 downregulated and 124 upregulated) were differentially expressed in yeast cells exposed to the 1 mg/L NP for 120 min, while 103 genes (56 downregulated and 47 upregulated) were differentially expressed for 180 min exposure. Meanwhile, 678 genes (168 downregulated and 510 upregulated) were differentially expressed upon exposure to 5 mg/L NP for 120 min, while 688 genes (215 downregulated and 473 upregulated) were differentially expressed upon exposure to 5 mg/L NP for 180 min. Although similar processes were affected by exposure to distinct BPA and NP concentrations, the number and magnitude of differentially expressed genes differ between low and high inhibition concentration treatments. Exposure to 300 mg/L BPA resulted in severe changes in the expression levels of several genes involved in oxidative phosphorylation, the tricarboxylic acid cycle, ribosomal activity, replication, and chemical responses. Besides, exposure to 5 mg/L NP resulted in substantial changes in the expression of several genes associated with oxidative phosphorylation, cell wall biogenesis, ribosomal biogenesis, RNA processing, heat shock proteins, and ubiquitin-conjugating enzymes. Conversely, small numbers of genes with slight changes in the expression were observed in cells exposed to low inhibition concentration of BPA and NP. These results demonstrate that yeast cells respond to BPA and NP in a concentration-dependent manner at transcriptional level via different genes and provide insight into the molecular mechanisms underlying the modes of action of BPA and NP.

Keywords: Bisphenol A, nonylphenol, transcriptional profiles, *Saccharomyces cerevisiae*, exposure

CLAIM FOR ORIGINALITY

The budding yeast, *Saccharomyces cerevisiae*, is a widely used eukaryotic model organism for analysis of several processes including cell cycle control, DNA repair, aging, gene expression, autophagy and the molecular and cellular pathways of human diseases, including cancer. The entire genome of this organism has been extensively annotated and characterized, and its genome shares many functional and structural similarities with higher eukaryotes, including humans. Approximately 30% of human genes associated with various diseases have yeast orthologs and also, many yeast genes are linked to several human disease genes. As such, this organism could potentially be used to clarify the molecular mechanisms and functional pathways involved in the cellular responses of higher eukaryotes to bisphenol A (BPA) and nonylphenol (NP) toxicity.

To date, although there are some studies performed to investigate the gene expression profiles on some organisms in response to BPA and NP, most of which consist of specific metabolic pathways, genes or gene groups analyzed by real time RT-PCR or DNA microarray. However, there is no study carried out on *Saccharomyces cerevisiae* which investigate the effects of BPA and/or NP. The main contribution of this study is that to provide the first analysis of genome-wide transcriptomic effects of exposure to both low and high inhibition concentrations of the environmental pollutants BPA and NP in the model organism *Saccharomyces cerevisiae*. The study addresses a topic that is of interest to the scientific community specifically to researchers in a range of fields, including toxicogenomics, transcriptomics, environmental science, and toxicology. Moreover, the study provides data at transcriptional level in the yeast model which may contribute with possible mechanistic insights of BPA and NP toxicity and may be meaningful as preliminary clues to orientate more complex studies in experimentally less accessible environmental microbial or higher eukaryotes.

Ceyhun BEREKETOĞLU **Prof. Dr. Bülent MERTOĞLU**

SYMBOLS

g **:** Gram

h **:** Hour

kg **:** Kilogram

Koc **:** Soil organic carbon-water partitioning coefficient

L **:** Liter

log **:** Logarithm

mg **:** Milligram

min **:** Minute

pKa **:** Negative base-10 logarithm of the acid dissociation constant

S **:** Solubility

µg **:** Microgram

ABBREVIATIONS

4-MBC : 4-Methylbenzylidene Camphor

ABC : ATP-Binding Casette

ATP : Adenosine Triphosphate

BPA : Bisphenol A

CDK : Cyclin-Dependent Kinase

DAVID : The Database for Annotation, Visualization and Integrated Discovery

DDT : Dichloro Diphenyl Trichloroethane

DEHP : Di(2-Ethylhexyl) Phthalate

DHA : Drug:H^+ Antiporter

DNA : Deoxyribonucleic Acid

EDC : Endocrine Disrupting Chemical

EDSTAC : Endocrine Disruptor Screening and Testing Advisory Committee

EDTA : Ethylenediaminetetraacetic Acid

ER : Estrogen Receptor

GO : Gene Ontology

GTP : Guanosine Triphosphate

HSP : Heat Shock Protein

IFN : Interferon

IL : Interleukin

IPCS : International Programme on Chemical Safety

LIMMA : Linear Models for Microarray Data

MDR : Multidrug Resistance

MFS : Major Facilitator Superfamily

NAD : Nicotinamide Adenine Dinucleotide

NCS : Neocarzinostatin

NP : Nonylphenol

NPE : Nonylphenol Ethoxylates

NR : Nuclear Receptor

OXPHOS : Oxidative Phosphorylation

PCR : Polymerase Chain Reaction

PDR **:** Pleiotropic Drug Resistance

PVC **:** Polyvinyl Chloride

RIN **:** RNA Integrity Number

RMA **:** Robust Multi-Array Average

RNA **:** Ribonucleotide Reductase

RNR **:** Ribonucleic Acid

SGD **:** Saccharomyces Genome Database

SPD **:** Spindle Pole Body

TCA **:** Tricarboxylic Acid Cycle

Tm **:** Melting Temperature

TNF **:** Tumor Necrosis Factor

USEPA **:** US Environmental Protection Agency

UV **:** Ultraviolet

YPD **:** Yeast extract-Peptone-Dextrose

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1. INTRODUCTION

One of the important problems faced by ecotoxicologists worldwide is the enormous challenge in evaluating of possible toxic effects and action mechanisms of chemicals which are derived from industrial and agricultural sources, found in a very high amount and diversity, and released continuously to the environment. Endocrine disrupting chemicals (EDC), one of the most important groups of these environmental toxic compounds, occur naturally or synthetically and may have serious effects on hormone biosynthesis, metabolism, homeostatic control or fertilization. Today, it is thought that there are thousands of EDCs, toxic effects of which are not known yet. Bisphenol A (BPA) and nonylphenol (NP) are two important EDCs that have high production rates worldwide and are widely used as building-blocks in several industrial applications. Although these two chemicals are considered to have some estrogenic effects on human bodies, their modes of action are still remaining unclear. Therefore, early detection in the environment and understanding the action mechanisms of BPA and NP, and development of in vitro and in vivo screening tools are of vital importance to identify and prevent their adverse effects on ecological system.

When current literature is evaluated, it is seen that studies on BPA and NP, until recent years, have focused on the identification of the presence or concentration of them in specific samples by using physical and chemical analytical measurements. Besides, recently, the importance of toxicological studies at the molecular level like measurement of gene expression profiles has been understood and some studies has been conducted in this area. In these studies, specific genes or some groups of genes that include small number of genes have been considered. However, the effects of these chemicals on cellular and metabolic processes have not been investigated at the level of transcriptome so far. In this thesis, it was aimed to investigate the effects of BPA and NP on the transcriptional profiles of single-celled model organism-*Saccharomyces cerevisiae* genome by using DNA microarray technology.

1.1. Endocrine disrupting chemicals

A wide variety of toxic chemicals found in the ecosystem exhibit structural resemblance to natural hormones and can accumulate within the human body (Kang et al., 2011). As a result, concern over the potential consequences of these chemicals on human health has increased over the past decade (Ferrer et al., 2011). Many of these toxic substances are endocrine disrupting chemicals (EDCs), which are naturally or synthetically occurring exogenous chemicals or mixture of chemicals that may change endocrine functions within the body by mimicking or interfering with endogenous hormones. Although there are various definitions for EDCs, Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), US Environmental Protection Agency (USEPA), and International Programme on Chemical Safety (IPCS) defined an EDC as "an exogenous chemical substance or mixture that alters the structure or function(s) of the endocrine system and causes adverse effects at the level of the organism, its progeny, populations, or subpopulations of organisms, based on scientific principles, data, weight-of-evidence, and the precautionary principle" (Roig et al., 2012; Zoeller et al., 2012; Rogers et al., 2013).

EDCs can show adverse effects at much low doses with acting through different mechanisms. Besides, high concentrations of these chemicals are continuously releasing to the environment through various human activities, such as industrial, agricultural and urban discharges worldwide. Not only the progress in analytical measurements, but also the development of extraction methods, such as gas and liquid chromatography combined with mass spectrophometry enable the detection of very low levels of these chemicals (Pedrouza et al., 2011). Moreover, it has been indicated that EDCs could cause complex effects on the human and wildlife environments and ecosystems at low doses (Kortenkamp, 2008). The level of the effect and mode of action of a chemical on human or natural habitat/population are associated with the nature of the chemical, such as structure, concentration, bioavailability, the physiological conditions of the organism, and exposure duration like bioaccumulation and low dose effect (Roig et al., 2012).

EDCs are able to exert their adverse effects through different mode of actions. For instance, EDCs can use several nuclear receptors (NR) and hormone receptors which are associated with sex hormones and also other steroids as mediators (Lazzati et al.,

2010; Rogers et al., 2013). Using these mediators and acting as agonists or antagonists in wide variety of human tissues such as lungs, brain, cardiovascular system, mammary glands, immune system, kidneys, liver, reproductive tracts (uterus, ovaries, testes, prostate), bones, and adipose and also other connective tissues, EDCs can change the expression of genes and the activity of their response elements, disrupt the interaction between natural hormones and their receptors, and also elevate the level of endogenous hormones by mimicking them (Mueller, 2004; Roig et al., 2012; Rogers et al., 2013). Although EDCs have been showed to have some adverse effects on sexual behavior and reproductions of wild animals, the effect of these chemicals on human reproductive system is still not clear (Falconer, 2006). Studies on the wildlife populations have showed that this group of chemicals may result in feminization of males, reproductive abnormalities, development of secondary sex characteristics and decreased fertility in females, neurological and developmental disorders, and deficiency in immune system (Colborn et al., 1993; DeRosa et al., 1998; Vos et al., 2000; Orlando and Guillette, 2007; Coppock, 2011).

EDCs can expose human and other organisms via a wide variety of sources. Among these sources, water and food which are contaminated with EDCs as a result of manufacturing plants and agricultural centers, food and beverage containers, respectively, are the primary routes for exposure to EDCs. EDCs are also found in pharmaceuticals, cosmetics, personal hygiene products and several other environmental sources such as sediments, wastewaters, surface waters, and groundwaters at a wide range of concentrations depending on the region and lifestyle (Roig et al., 2012; Rogers et al., 2013).

EDCs refer to a broad class of chemicals found in thousands of products such as plastics and plasticizers, alkylphenols, fuels, pesticides, personal care products, polychlorinated biphenyls, dioxins, polycyclic aromatic hydrocarbons, and several compounds in use (Diamanti-Kandarakis et al., 2009; Roig et al., 2012). A list of some important EDCs is summarized in Table 1.1. Of these chemicals, bisphenol A (BPA) and nonylhenol (NP) which are well-known, widely used, and two of the most important EDCs are investigated in the present study.

Table 1.1 Examples of EDCs, their classes, and some of their sources

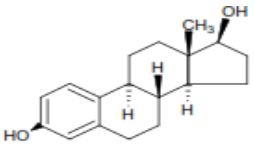
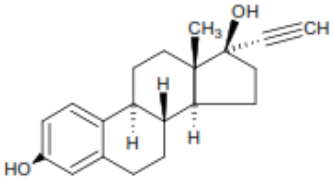
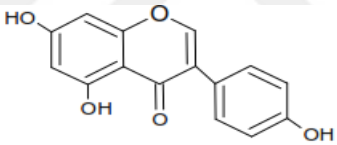
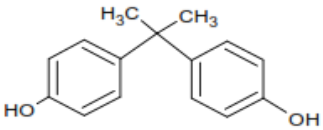
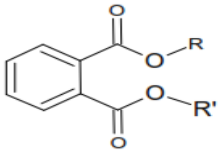
Class	Example of substances	Chemical structure	Sources
Endogeous hormones	**Estradiol** pKa: 10.5–10.7 logP: 4.01 S: 3.6 mg/L		Humans and animal bodies
Synthetic estrogen	**Ethynylestradiol** pKa: n.a logP: 3.67 S: 11.3 mg/L		Chemically synthesized and main components in oral contraceptive pills for birth control and hormone therapy
Phytoestrogen	**Genistein** pKa: 7.08 logP: 3.67 S: weak		Natural organic compound found in a number of plants including lupin, fava beans, soybeans
Plasticizers and surfactants	**Bisphenol A** pKa: 9.73 logP: 3.67 S: 120-300 mg/L		Production of polycarbonate plastic, epoxy resine
	Phthalates: DEHP pKa: n.a. logP: 4.89 S: 0.285 mg/L		Plastic products, PVC

Table 1.1 continued

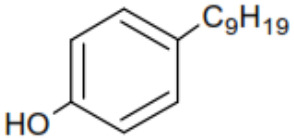
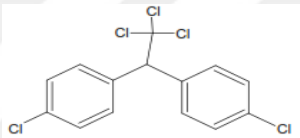
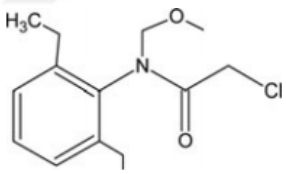
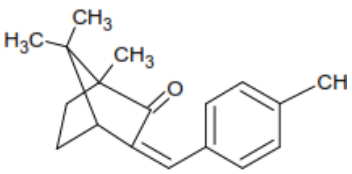
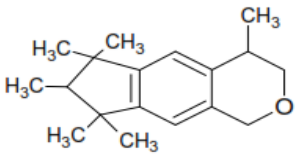
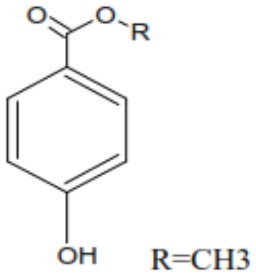
Pesticides	**Alkylphenol: Nonylphenol** pKa: 10.25 Log P: 5.71 S: 6.35 mg/L		Non ionic surfactant in domestic and industrial applications, laboratory detergents, antioxidant, plastic stabilizers
	DDT and metabolites (Insecticide) pKa = n.a logP:6.91 S: 0.025 mg/L		Synthetic organochloride insecticide
	Alachlor (Herbicide) pKa = 0.62 logP: 3.09 S: 242 mg/L		Herbicide used mainly to control annual grasses and broadleaf weeds in corn (maize), soybeans, and peanuts
UV Screen	**4-MBC** pKa = n.a. logP: 5.1 S: 0.04–1.3 mg/L		Organic camphor derivative used in sunscreen lotions and other skincare products to protect the skin against UV, specifically UV B radiation

Table 1.1 continued

Musks	**HHCB** pKa = n.a. logP: 5.9 S: 1.75 mg/L		Detergent and cosmetic compositions, fragrance, perfume
Parabens	**Methylparaben** pKa: 8.4 logP: 1.96 S: 2.5 g/L		Chemicals widely used as preservatives in shampoos, makeup, shaving gels, personal lubricants, toothpaste pharmaceuticals, spray tanning solution, and commercial moisturizers

1.1.1. Bisphenol A (BPA)

BPA, a well-known hormone-like chemical belonging to the wider family of diphenylalkanes, is commonly used as a monomer in the production of epoxy resins and polycarbonates, and as a plasticizer in polyvinyl chloride (Pupo et al., 2012; Singh and Li, 2012). Epoxy resins line the inner surface of food and beverage cans and water pipes, while polycarbonates are widely used in plastic containers such as water and baby bottles (Ferrer et al., 2011; Alonso-Magdalena et al., 2012). BPA is also used as a monomer for dental products and other items used in daily life and as a plasticizer to soften and increase the flexibility of polyvinyl chloride products (Alonso-Magdalena et al., 2012; Pupo et al., 2012). Each year, greater than six billion pounds of BPA are produced worldwide, and more than 100 tons leach into the environment via different routes such as from sewage sludge used in agriculture, effluent of wastewater treatment plants, and use of various products and their disposal in landfill (Vanderberg et al., 2009; Kang et al., 2011; Alonso-Magdalena et al., 2012; Huang et al., 2012; Careghini

et al., 2015; Corrales et al., 2015). In 2010, Canada was the first country accepted that BPA is a toxic substance, and restricted the use of it in baby bottles. In 2011, Use of BPA in baby bottles was restricted in Europe. Moreover, it has been shown that BPA leached into the baby bottles at high temperature (Kubwabo et al., 2009; Rogers et al., 2013).

BPA is considered an EDC due to its ability to mimic estradiol by promoting estrogenic activity through the binding and activation of estrogen receptors (i.e., ERα and ERβ) (Vanderberg et al., 2009; Pupo et al., 2012). Although this activity is approximately 10,000-fold weaker than that of estradiol, many studies have shown that BPA triggers receptor responses and also acts as an androgen receptor (Flint et al., 2012). Based on these results, many studies of the effects of BPA have focused on endocrine systems. However, because BPA is constantly released to the environment and its adverse effects occur via different routes, it is critical to examine the modes of action of this compound.

Environmental fate of BPA

Understanding the environmental fate and determining the levels of BPA in ecosystems are crucial to find out its potential risks on the populations and develop strategies for reducing its exposure rates and toxicological effects. BPA is a moderately water-soluble chemical and its hydrolysis is negligible under ambient conditions due to lack of hydrolysable groups. It is a moderately bioaccumulative compound (Careghini et al. 2015). Under aerobic conditions, BPA has been shown to be biodegraded both in soil and sediments. Half-lives of BPA in soils have been observed to be between 3 and 37.5 days. On the other hand, no BPA degradation has been detected in anaerobic soils and anoxic estuarine sediments after experiments last for 70 and 120 days, respectively (Flint et al., 2012; Yu et al., 2013; Chang et al., 2014; Yang et al., 2014; Careghini et al., 2015).

Reported concentrations of BPA ranged between 0.55 and 147 μg/kg on dry weight basis (d.w.) in soils, <0.24 and 492 μg/kg d.w. in sediments, 0.001 and 20 μg/L in groundwater and <0.001 and 92 μg/L in surface water (Careghini et al., 2015). Moreover, higher concentrations of BPA have been detected in the sludge of wastewater treatment plants receiving elevated industrial effluent as >100 mg/kg (Meesters and

Schroder, 2002) and in hazardous waste landfill leachate as 17.2 mg/L (Yamamoto et al., 2001). Several studies have analyzed the migration of BPA from polymer packaging food, and BPA concentrations have been reported up to 790 μg/kg on fresh weight basis (f.w.) in food (Noonan et al., 2011), 42.6 g/kg in thermal receipt paper (Babu et al., 2015), 26.6 mg/kg in food-contact paper (Suciu et al., 2013), and 0.86 μg/L in drinking waters/commercial drinks (Careghini et al., 2015). 50 mg/kg BPA has been determined as "low" dose in different toxicological studies carried out in vivo (Alonso-Magdalena et al., 2010; Wang and Bennett, 2012) and experiments were conducted with concentrations up to 200 mg/kg to analyze the effects of BPA (Xi et al., 2011; Tan et al., 2013). Although BPA is biodegradable in soil and sediments under aerobic conditions (Careghini et al., 2015), it can accumulate in natural environments due to its high production and release rate compared to removal rate, making it a potential threat to ecosystems (Careghini et al., 2015; Zhou et al., 2016).

1.1.2. Nonylphenol (NP)

NP is a well-known environmental estrogen involved in organic compounds called alkylphenols, and produced by industrial processes during the alkylation process of phenols (Carlisle et al., 2009; Careghini et al., 2015; Lu et al., 2015). The addition of ethoxyl groups to the compound produces nonylphenol ethoxylates (NPE), widely used as a building block of non-ionic surfactants that are used in various household and industrial applicaions such as detergents, emulsifiers, dyes, plastics, cosmetics, lubricant oils, construction materials, and vulcanized rubber, and production. It is also used in the production and processing of pharmaceuticals, agricultural chemicals, textiles, fuels, petroleum, metals, leather, and paper pulp (Brooke et al., 2005; Carlisle et al., 2009; Lu et al., 2015). In 2010, the demand for NP by U.S. was estimated to be 380 million pounds (USEPA, 2010b; Careghini et al., 2015). Besides, the consumption volume of NPE surfactants in U.S. and Canada was also estimated between 300 and 400 million pounds per year (USEPA, 2010b).

NP mimics the natural hormone 17β-estradiol and interferes with estrogen receptors and can disrupt or change the endogenous estrogen functions at different reproductive and development stages. It has been reported that NP was used as an agent in contraceptive spermicidal applications (Brooke et al., 2005). Moreover, NP has been

found in human breast milk, serum, blood, adipose tissue, and urine recently (Roig et al., 2012). These observations led European countries to take actions againist nonylphenol and its derivatives and they have been accepted as priority hazardous substances and also their uses are currently being regulated. However, China, India and several South American countries, and also many other countries are still producing and using these molecules in high volumes and they take no any action to regulate their usage (Soares et al., 2008).

Environmental fate of NP

NP is a viscous liquid with a light pale colour at room temperature (Soares et al., 2008; Careghini et al., 2015). Although significant amounts of NP and its derivatives are directly released into the environment by the industrial applications including the discharge municipal and industrial wastewaters into surface waters, the biodegradation of NPEs by decreasing of ethoxy groups in the landfills, wastewater, and sewage treatment plants as well as sludge recycling facilities is the main source of NP to the environment (Soares et al., 2008; Lu and Gan, 2014; Careghini et al., 2015). This degradation commonly occurs under anaerobic condition even it has been shown under aerobic conditions (Careghini et al., 2015). NP is a hydrophobic chemical with high log K_{oc} value, low water solubility and mobility, and these physical-chemical properties play a crucial role on NP degradation and transport in soil-water systems and river sediments by limiting its spreading (Soares et al., 2008; Careghini et al., 2015). NP has been reported as moderately bioaccumulative compound (OEHHA, 2009). Half-lives of NP isomers in river sediments have been showed to be between 0.9 and 13.2 days under oxic conditions, while this time could be between 15.1 and 20.1 days under slightly anoxic conditions (Lu and Gan, 2014). It has also been indicated that first-order half-lives of NP isomers could be longer than 200 days under reduced conditions (Careghini et al., 2015).

Reported concentrations of NP ranged between 0.01 and 0.98 μg/kg d.w. in unamended soils, soils fertilized with manure, or with limited amounts of sewage sludge in soils, 3.6 μg/kg d.w. and 72 mg/kg d.w. in sediments, 0.001 μg/L and 3.85 μg/L in groundwater and 3×10^{-4} and 37.3 μg/L in surface water (Careghini et al., 2015). Detected high concetrations of NP have been commonly related to particular locations

close to industrial districts such as tannery and textile industries, domestic wastewater discharges or wastewater treatment plant effluents where high population density found (Azevedo et al., 2001; Kannan et al., 2003; Cespedes et al., 2005; Duan et al., 2014; Stewart et al., 2014). Besides, the present of NP in biota, food, and bottle water have been also investigated. Found NP concentrations have spanned between 0.1 and 100 μg/kg fresh weight basis (f.w.) in different foods, <7.7 ng/L and 0.30 μg/L in drinking waters/commercial drinks, and 0.1 and 19.4 μg/kg f.w. in packed foodstuff purchased from supermarkets in Germany (Guenther et al., 2002; Careghini et al., 2015). It has been reported that the average intake of NP from foods ranges between 0.067 and 0.370 μg/kg/day for adults (Careghini et al., 2015), while the average intake of NP from drinking bottled water has been calculated to be between 0.36 and 0.60 μg/day for humans (Loyo-Rosales et al., 2004; Careghini et al., 2015).

1.2. Toxicogenomics

Studies on EDCs, until recently, have focused on the identification of the presence or concentration of chemicals in specific samples by using physical and chemical analytical measurements. However, thanks to the recent developments in the field of functional genomics, a new methodology which is called toxicogenomics that combines genomic tools with bioinformatics has arised. Toxicogenomics involves the application of genomic methodologies to the study of toxicology and could facilitate the identification and characterization of cellular responses to toxicants at various molecular levels, such as genomic, transcriptomic, proteomic, and metabolomics levels (Pina and Barata, 2011; dos Santos and Sa-Correia, 2015).

Transcriptomics is a discipline that simultaneously analyzes whole mRNA transcripted at a certain physiological or developmental state of a cell. Evaluating transcripts is crucial to interpret functional elements of the genome, determine molecular components of cells and tissues, and possible effects of toxic chemicals (Momose and Iwahashi, 2001; Yu et al., 2010; Gil et al., 2011). Various methods have been developed to determine and analyze transcriptional profiles such as hybridization and sequencing. DNA microarray is a hybridization-based method which is an important tool in toxicogenomics. It also becomes important in determining gene expression levels, and in revealing and evaluating possible toxic effects of such

chemicals because it is possible to analyze thousands of gene expression profiles within a single hybridization (Wang et al., 2004; Moens et al., 2006). DNA microarray was first used in 1996 and to date; it has been used in several fields, such as molecular biology, medical research, and diagnostic. Nowadays, expression profiles based on this technology are used to diagnose various cancers, determine treatment recipes and analyze the effects of new drugs. Moreover, recently, the necessity to identify the effects of chemicals like EDCs at the molecular level has been understood and use of DNA microarray technology in investigating environmental chemicals has begun (Wang et al., 2004; Lettieri, 2006; Yum et al., 2010)

1.3. Saccharomyces cerevisiae

The budding yeast *Saccharomyces cerevisiae* (*S. cerevisiae*) is widely used as a eukaryotic model organism for analysis of several processes such as cell cycle control, DNA repair, aging, gene expression, autophagy and the molecular and cellular pathways of human diseases, including cancer (Nielsen, 2009; Lindstrom et al., 2011; Chen and Burgoyne, 2012; Matuo et al., 2012**)**, owing to its simple growth conditions (easy manupilation and inexpensive cultivation), rapid reproductive rates (doubling in two hours), and the ease with which it can be manipulated. Moreover, the entire genome of this organism has been annotated and characterized, and the data have been deposited in freely available databases (Momose and Iwahashi, 2001; Takumi et al., 2010; Gil et al., 2011).

The *S. cerevisiae* genome includes both functional and structural similarities with those of higher eukaryotes, particularly humans. To date, approximately 30% of human genes associated with various diseases have yeast orthologs and also, many yeast genes are linked to several human disease genes. Studies on yeast *S. cerevisiae* have aid in understanding some aspects of human diseases including type 2 diabetes, Werner's syndrome, and several types of cancers. As such, this organism could potentially be used to clarify the molecular mechanisms and functional pathways involved in the cellular responses of higher eukaryotes to EDCs toxicity (Matuo et al., 2012; Nomura et al., 2013).

1.4. Gene expression studies

There are several studies performed to investigate the gene expression profiles of organisms in response to EDCs including BPA and NP, but most of which consist of specific genes analyzed by real time RT-PCR (Kazeto et al., 2004; Yamaguchi et al., 2005; Zhang et al., 2005; Jin et al., 2009; Jin et al., 2010; Kang et al., 2011; Liu and Sung, 2011; Liu et al., 2012; Park and Kwak, 2013; Park and Kwak, 2104; Ribeiro-Varandas et al., 2014; Sun et al., 2014; Rajakumar et al., 2015; Balbi et al., 2016; Hayes et al., 2016; He et al., 2016; Kazemi et al., 2016; Qiu et al., 2016; Yuan et al., 2016). In addition, there are some studies focusing on specific metabolic pathways, genes or gene groups by using DNA microarray technology (Hoyt et al., 2003; Hong et al., 2006; Moens et al., 2006; Kausch et al., 2007; Takamiya et al., 2007; Baker et al., 2009; Boehme et al., 2009; Park et al., 2010; Choi et al., 2011; Kim et al., 2011; Lawson et al., 2011; Robertson and McCormick , 2012; Schiller et al., 2013; Won et al., 2014; Tait et al., 2015). Although most of the studies have usually focused on aquatic organisms, such as medaka, minnow, salmon, chinese sturgeon, mussel, and *Cyprinus carpio,* there have been some studies carried out on various animal and human cell lines. On the other hand, no study has been conducted to analyze the gene expression profiles of *S. cerevisiae* in response to BPA or NP so far.

1.4.1. Gene expression studies on aquatic organisms

Zebrafish, a model organism, has been used in some studies which focused on the effects of NP on gene expression profiles of several genes using real time RT-PCR. In one of these studies, the effects of NP on the several genes associated with immune system (*TNF-α, IFN*, *IL-1β, IL-8*) in the early developmental stage of zebrafish have been investigated and it has been observed that various concentrations of NP showed different effects (Jin et al., 2010). In another study conducted by Jin et al., (2009), vitellogenenin gene expression profiles in the embryo, larval, juvenile and adult life stages of zebrafish exposed to NP has been analyzed and it has been observed that NP did show effect on embriyo, juvenile and adult stages. Kazeto et al., (2004) has studied the effect of NP on the cytochrome P450 aromatase gene which is responsible for the conversion of androgens to estrogens of zebrafish juveniles using quantitative RT-PCR and has showed that NP affects development and reproductive physiology in a dose-

dependent manner. Moreover, several other aquatic organisms have been used to analyze the transcriptional effect of BPA and NP using real time RT-PCR. In the rare minnow, the effects of BPA on DNA methylation (Yuan et al., 2016) and steroidogenic enzyme genes (Liu et al., 2012); in medaka, the effects of BPA on the immune-responsive genes (Qiu et al., 2016), a set of genes associated with the hypothalamic–pituitary–gonadal axis (Sun et al., 2014), and estrogen-responsive genes such as vitellogenin I, vitellogenin II and alpha-type estrogen receptor genes (Yamaguchi et al., 2005); in chinese sturgeon, the effect of NP on gene expression level of vitellogenin gene (Zhang et al., 2005); in marine mussels, the effect of BPA on 13 genes involved in different biological processes (Balbi et al., 2016); in paddle crabs *Charybdis japonica*, the effects of BPA and 4-NP on *HSP70* and *HSP90* gene expressions (Park and Kwak, 2013; Park and Kwak, 2014); in aquatic crustaceans, *Neocaridina denticulata*, the short-term effect of NP on different functional classes genes using semi-quantitative RT-PCR (Liu and Sung, 2011) have been investigated.

DNA microarray technology has also been used to to study gene expression profiles of various aquatic organisms in several studies. Schiller et al., (2013) have analyzed the transcriptomic alterations of zebrafish exposed to BPA and have found that BPA induced a biological process which is called the response to xenobiotic stimulus. Kausch et al., (2007) have studied the effect of BPA on male zebrafish using arrays consisting of 14000 oligonucleotides and observed that BPA induces gene expression of *VTG-1* gene. In another study performed with zebrafish embriyos treated with NP, it has been reported that a group of genes could be an indicator for NP (Hoyt et al., 2003). Moreover, Baker et al., (2009) has researched the effects of NP on laboratory male zebrafish and wild hornyhead turbot. For this purpose, a multi-gene cross microarray has been developed using genes that are involved in the actions of adrenal and sex steroids, thyroid hormone, and xenobiotic responses, and it has been reported that this multi-species microarray could be useful for investigating endocrine responses in other fish. In addition, gene expression profiles of livers of juvenile carp exposed to BPA and NP have been studied using a custom made cDNA array including 860 hormon and sex-related genes (Moens et al., 2006). In addition, the effect of 4-NP on gene expression profiling of the liver tissue of the marine medaka fish, *Oryzias javanicus*, was examined using HazChem Fish Array Ver. 02 cDNA microarray consisting of a set of 2425 cDNA

clones (Won et al., 2014). Moreover, Robertson and McCormick, (2012) have analzyed the gene expression profiles of Atlantic salmon smolts exposed to NP using GRASP 16K cDNA microarrays and found that NP altered the expression of several features in the liver.

1.4.2. Gene expression studies on other eukaryotes

Mouse and rat, two important model organisms, have been used in various studies to investigate the effects of BPA and NP on gene expression profiles. He et al., (2016) have used adult male mice treated with BPA to evaluate gene expression of cytokines and chemokines genes using real time RT-PCR. They have found that BPA increased the mRNA expression of several genes. Kang et al., (2011) have treated pregnant mice by BPA to screen for possible epigenetic perturbations caused by BPA at imprinted loci. Then, they have isolated RNA from the placenta, yolk sac, amnion, head, body, heart, liver, lung, stomach, and intestines and measured the allele-specific expression of 38 imprinted transcripts by reverse-transcription PCR SNuPE assays. They have reported that the imprinted genes are insensitive to BPA. In another study carried out by Lawson et al., (2011), the gene expression changes in the fetal mouse ovary exposed to BPA have been analyzed to understand the impact of BPA using microarray analysis, and observed significant changes in gene expression in the fetal ovaries. In another study, pregnant mice have been exposed to BPA, their placenta has been taken, and microarray analysis has been performed. It has been shown that different concentration of BPA showed different effects on placental morphology and development (Tait et al., 2015). Moreover, the effects of BPA on mouse Leydig tumor cell line (Takamiya et al., 2007) and the effects of NP on miRNA regulation using mouse sertoli TM4 cell line (Choi et al., 2011) have been carried out using microarray. On the other hand, the effects of various doses of BPA on hepatic oxidative stress-related gene expression in rats have been investigated using real time PCR. It has been shown that BPA increased the antioxidant gene expression that causes hepatotoxicity (Kazemi et al., 2016). Besides, Hong et al., (2006) have studied the effects of NP and BPA on the uterus of immature rats by using a custom microarray consisting of 7636 genes.

Human cell lines have also been used to analyze the the effects of EDCs on gene expression patterns of several genes. Ribeiro-Varandas et al., (2014) have investigated

the effects of BPA on HT29 human colon adenocarcinona cell line and human umbilical vein Endothelial cells using quantitative real time PCR. It has been shown that BPA induces global transcription deregulation of long interspersed element-1 in both cell lines. Rajakumar et al., (2015) have analyzed the effects of BPA on the expression of several human placental genes using trophoblast cells and quantitative real time PCR, and they have indicated that BPA may contribute to altered placental function. Moreover, Hayes et al., (2016) have examined the effect of BPA on the expression of histone-modifying enzymes using human ovarian cancer cell lines by real time PCR. In another study carried out by Park et al., (2010), the effects of BPA on the gene expression profile of human hepatocellular cell line have been investigated. For this purpose, a custom-made HazChem human array V3 consisting of 1136 genes has been used and several genes associated with homeostasis, coagulation, wound healing, angiogenesis, cell redox homeostasis, and cell proliferation have been found to be induced. In addition, Boehme et al., (2009) have examined gene expression profiles in estrogen receptor (ER)-proficient Ishikawa plus and ER-deficient Ishikawa minus endometrial cancer cells exposed to BPA and showed that BPA has both estrogenic and anti-estrogenic effects. Besides, Kim et al., (2011) have exposed MCF-7 cells with BPA and NP and analyzed their effects using human c-DNA microarray including 416 endocrine system related genes.

1.4.3. Gene expression studies on *S. cerevisiae*

S. cerevisiae has not been used to study the effects of BPA and NP on gene expression profiles by microarray or real time PCR so far. However, several studies have been carried out to evaluate the expression profiles of yeast cells exposed to various chemicals such as p-anisaldehyde, vanillin, neocarzinostatin (NCS), alachlor, cadmium, nickel chloride, polystyrene latex nanoparticles, amphotericin B and nystatin. These previous studies have demonstrated that certain compounds effectively induce or repress several genes associated with many different biological processes including DNA damage and repair, chemical-response, iron and copper acquisition, ribosomal activity, nucleobase-containing metabolic processes, and oxidative phosphorylation (OXPHOS), and defects in most of which in higher eukaryotes may cause some important disorders. (Tamai et al., 1992; Momose and Iwahashi, 2001; Schaus et al., 2001; Zhang et al.,

2002; Takumi et al., 2010; Yu et al., 2010; Gil et al., 2011; Nomura et al., 2013).

Considering that organisms can respond to environmental toxic compounds with the interactions of different cellular and metabolic processes, modes of action of BPA and NP were investigated by using DNA microarray technology on a single-celled model organism-*S. cerevisiae* which has simple growth conditions can be easy cultured and shares the complex internal cell structure of higher eukaryotes. Therefore, genome-wide transcriptional changes in *S. cerevisiae* BY4742 upon exposure to BPA and NP were analyzed to identify differentially expressed genes and cellular mechanisms, including biological processes, metabolic pathways, and cellular compartments, affected by these compounds. For these analyses, in this study, it has been focused on two exposure scenarios: (1) exposure to a low inhibition concentration (resulting in <6% inhibition in cell number for BPA and <15% inhibition in cell number for NP), and (2) exposure to a high inhibition concentration (resulting in >70% inhibition in cell number for BPA and >65% inhibition in cell number for NP).

2. MATERIALS AND METHODS

2.1. Strain, growth conditions, and chemical exposure

S. cerevisiae BY4742 (Matα; his3Δ1; leu2Δ0; lys2Δ0; ura3Δ0) was obtained from the Euroscarf collection (Frankfurt, Germany). To obtain single colonies, prepared yeast extract-peptone-glucose (YPD) agar (2% [w/v] D-glucose, 2% [w/v] peptone, 1% [w/v] yeast extract, 1% [w/v] agar) plates were spread with stock yeast cells using sterile loop and incubated at 30°C for 48 h. Unless otherwise stated, cells were cultured at 30°C with orbital shaking (180 rpm). For pre-cultures, 25 mL of yeast extract-peptone-glucose (YPD) medium (2% [w/v] D-glucose, 2% [w/v] peptone, 1% [w/v] yeast extract) was inoculated with a single colony of cells obtained from YPD plates and incubated overnight. A volume fraction of 1% of the pre-culture was then used to inoculate 100 mL YPD in 500-mL flasks and grown to an optical density at 600 nm (OD_{600nm}) of 0.8 ± 0.05 (mid-exponential phase). Subsequently, BPA and NP stock solutions were prepared in ethanol separately and various final concentrations of them were added to the cultures. 1, 5, 25, 50, 75, 100, 120, 140, 160, 200, 250, and 300 mg/L BPA were the final concentrations of BPA that were added to the cultures, while 1, 3, 5, 7.5, 10, and 20 mg/L NP were the final concentrations of NP that were added. The final concentration of ethanol in the medium was maintained at 1% (v/v), which did not affect growth. Other cultures containing 1% (v/v) ethanol, but lacking BPA and NP were used as the controls.

To determine the inhibition rates after BPA and NP exposures, and appropriate concentrations of them, cell viability was measured by vital staining with methylene blue solution (0.01% methylene blue, 2% sodium citrate), according to previously described methods (Winter et al. 1997). Briefly, aliquots of yeast cultures exposed to BPA for 3 h beginning from addition of the chemical were taken, suitably diluted, and mixed with an equal volume of methylene blue solution. The number of dead (stained blue) and live (unstained) cells were determined microscopically within 10 min after mixing. The same procedure was applied for NP except that aliquots were taken after 2 and 3 h exposure intervals. The percentage of inhibition of yeast growth (under sublethal doses of BPA and NP) was defined as $[(N^0 - N^x)/N^0] \times 100$, where N^x and N^0 are the numbers of yeast cells in the culture containing X mg/L of either BPA or NP and

in that lacking BPA or NP, respectively. Inhibition rates were categorized as low (<6% inhibition in cell number) and high (>70% inhibition in cell number) for BPA, while the low and high inhibition rates for NP were categorized as <15% and >65% inhibition in cell number, respectively. One concentration appropriate for each category was determined for further analyses. The growth curve for the selected BPA and NP concentrations was constructed by monitoring optical density at 600 nm. Briefly, culture samples were taken every 2 h, suitably diluted (to keep the absorbance value smaller than or equal to 0.600 nm which the highest value for linearity of spectrophotometer device), and optical density was measured using spectrophotometer (Hacha-Lange, Lovelang, Colorado, US). All the optical density measurements were duplicated and each growth curve construction experiment was performed at least twice. Besides, three independent toxicity experiments were performed for each concentration. Finally, samples were harvested for microarray analysis, immediately flash-frozen in liquid nitrogen and stored at -80°C until the RNA isolation step.

2.2. RNA isolation and DNA microarray analysis

RNA isolation was performed following the modified enzymatic lysis protocol provided with the RNeasy Mini Kit (Cat no: 74104; Qiagen, Venlo, Netherlands). Briefly, harvested cells were resuspended in 100 µL enzyme-containing Buffer Y1 (1 M sorbitol, 0.1 M EDTA at pH 7.4, before use: 0.1% β –mercaptoethanol and 150 U lyticase were added), and incubated for 30 min at 30°C with gentle shaking. 350 µL Buffer RLT was added to each tube and vortexed vigorously. Then, 250 µL pure ethanol was added to the lysate and tubes were mixed by pipetting. Following this, approximately 700 µL sample was applied to each an RNeasy mini spin column sitting in a 2 ml collection tube and then, tubes were centrifuged for 15 sec at 8000xg, flow-through was discarded. For washing, 700 µL Buffer RW1 was applied to each RNeasy column, and tubes were centrifuged for 15 sec at 8000xg. RNeasy columns were transferred into new 2 mL collection tubes, 500 µL Buffer RPE was added onto RNeasy columns, and tubes were 15 sec at 8000xg. Flow-through was discarded, and this step was repeated. Tubes were then centrifuged for 2 min at maximum speed to dry RNeasy membranes. Finally, RNeasy columns were transferred into 1.5 mL collection tubes, 50 µL RNase-free water was applied onto RNeasy membrane, and tubes were centrifuged

for 1 min at 8000xg. A NanoDrop ND-100 UV-vis spectrophotometer (Thermo Fisher Scientific Inc., Waltham, MA, USA) was utilized to analyze the quantity and quality of the resulting RNA samples. RNA integrity (RIN) was estimated using a Agilent Bioanalyzer 2100 (Agilent Technologies, Santa Clara, CA, USA) device with an RNA 6000 Nano Assay kit (Agilent Technologies), and only those samples with RIN values of 7–10 were used for further analysis.

Approximately 100 ng of each total RNA sample was then used to synthesize first-strand cDNA, which was converted into double-stranded DNA using a GeneChip 3′ IVT Express Kit (Affymetrix, Inc., Santa Clara, CA, USA). Briefly, for each individual sample, 5 μL Total RNA/poly-A RNA Control Mixture which contains total RNA sample (100 ng), diluted poly-a RNA controls and nuclease-free water was prepared on ice. Then, first-strand master mix which contains 4 μL first-strand buffer mix and 1 μL first-strand enzyme mix was prepared and added to individual tubes, and subsequently, 5 μL of the Total RNA/poly-A Control Mixture was added. Tubes were incubated for 2 h at 42°C for first-strand cDNA synthesis. Following the first-strand cDNA synthesis, second-strand master mix which contains 13 μL nuclease-free water, 5 μL second-strand buffer mix, and 2 μL second-strand enzyme mix for each tube was prepared on ice and then, transferred to each 10 μL first-strand cDNA tubes. Tubes were incubated for 1 h at 16°C followed by 10 min at 65°C in a thermal cycler to synthesize second-strand cDNA.

in vitro transcription and synthesis of biotin-labeled antisense RNA (aRNA) were performed using the double-stranded cDNA as a template. Briefly, IVT master mix which contains 4 μL IVT biotin label, 20 μL IVT labeling buffer, and 6 μL IVT enzyme mix for each sample was prepared at room temperature, subsequently transferred to 30 μL double-stranded c DNA sample. Then tubes were incubated for 16 h at 40°C.

The final product was purified and quantified using a NanoDrop ND-100 UV-vis spectrophotometer (Thermo Fisher Scientific). The purification and fragmentation steps were performed using GeneChip reagents, and fragmented aRNA was assessed with the Agilent 2100 Bioanalyzer (Agilent Technologies).

The purification step consisted of three steps which were aRNA binding, washing the beads, and aRNA elution respectively. For aRNA binding, aRNA binding mix

which contains 10 µL RNA binding beads and 50 µL aRNA binding buffer concentrate for each sample was prepared and then added to samples and mixed. 120 µL ultrapure ethanol was added to each sample, mixed and shaken for 2 min. Tubes were then placed on the magnetic stand and beads were captured for 5 min. While tubes were on the stand, supernatant was carefully discarded. Then tubes were removed from the stand. For washing the beads, 100 µL aRNA washing solution was added to each sample, and samples were shaken for 1 min. Tubes were placed on the magnetic stand as previously described. Then, supernatant was carefully discarded and tubes were removed from the stand. Washing steps were repeated once again. Finally, tubes were moved to shaker and shaken vigorously for 1 min to evaporate the residual ethanol. For aRNA elution, 50 µL preheated to 60°C aRNA elution solution was added to each sample and shaken vigorously for 3 min. Tubes were placed on the magnetic stand and beads were captured. Supernatants containing eluted aRNAs were transferred to nuclease-free PCR tubes. Obtained aRNA samples were quantified using a NanoDrop ND-100 UV-vis spectrophotometer (Thermo Fisher Scientific). The fragmentation was started by preparing 20 µL aRNA fragmentation mixture which contains variable amount of aRNA equal to 7.5 µg, 4 µL 5x array fragmentation buffer, and variable amount of nuclease-free water for each sample and incubated for 35 min at 94°C. Then samples were assessed with the Agilent 2100 Bioanalyzer (Agilent Technologies).

Affymetrix Yeast 2.0 arrays were prepared for hybridization with the reagents supplied in the GeneChip Hybridization, Wash, and Stain Kit (Affymetrix, Inc.). A total of 5 µg of aRNA was hybridized to the arrays for 16 h at 45°C. For washing and staining, the arrays were loaded into a fluidics station using the Affymetrix Command Consoles Software (AGCC) 3.0.1 Fluidics Control Module with the Mini-Euk 2v3 protocol. Finally, arrays were scanned on an Affymetrix GeneChip Scanner 3000 device. Independent biological triplicates were processed and analyzed for each exposure condition and control.

2.3. Microarray data analysis

CEL files obtained from the analyzed arrays were subjected to quantile normalization using RMA (Bolstad et al. 2003) implemented in the affy package (Gautier et al. 2004) of the R/Bioconductor suite of tools (Gentleman et al. 2004) for data analysis.

Differentially expressed genes were identified from the normalized log-expression values using the multiple testing option of LIMMA (Smyth 2004). A p-value threshold of 0.01 and a no fold-change cutoff were used to identify differences in gene expression between the low inhibition concentration exposure level and the control group, while genes with a fold-change cutoff of 1.5 were considered significantly differentially expressed for the high inhibition concentration group. Genes satisfying both p-value and fold-change thresholds were considered differentially expressed for each exposure level with respect to the control. Genes exhibiting statistically significant changes in expression were used as inputs for the gene set enrichment analysis based on Gene Ontology (GO) annotations. All GO enrichment analyses were performed via GO Slim Mapper using the *Saccharomyces* Genome Database (SGD), with a maximum p-value of 0.05. Clustering analysis of significantly enriched biological processes was performed using the CIMminer (Scherf et al. 2000) and presented as a heat map. Functional annotation for pathway analysis was conducted using DAVID Bioinformatics Database (https://david.ncifcrf.gov/home.jsp) and the p-value was corrected using the Benjamini-Hochberg method. Common genes were found by comparing BPA and NP results and also by comparing the results of low and high inhibition concentrations of EDC, and presented using Jvenn diagram.

2.4. Quantitative real-time reverse transcription (RT)-PCR

For quantitative real-time RT-PCR analyses, cDNA was synthesized from equivalent amounts of the total RNA samples used in the microarray experiments, respectively, using a QuantiTect Reverse Transcription Kit (Qiagen, Valencia, CA, USA), according to the manufacturer's instructions. Briefly, RNA samples which were at the same concentrations were thawed on ice, while gDNA Wipeout Buffer, Quantiscript Reverse Transcriptase, Quantiscript RT Buffer, RT Primer Mix, and RNase-free water were thawed at room temperature and stored on ice. According to the number of samples, a master mix for total genomic DNA elimination reaction (2 µL gDNA Wipeout Buffer and appropriate amount of water considering the concentration of RNA samples which should be between 10 pg and 1 µg) was prepared. Then the master mix was distributed to the tubes and RNA samples were added. Tubes were incubated for 2 min at 42°C and then placed on ice immediately. After that, appropriate amount of reverse-transcription

master mix consisting of 1 µL Quantiscript Reverse Transcriptase, 4 Quantiscript RT Buffer, and 1 µL RT Primer Mix for each tube was prepared on ice. Then 6 µL of master mix was distributed to each tube and 14 µL template RNA was added and mixed. Subsequently, tubes were incubated 15 min at 42°C for cDNA synthesis and 3 minuted at 95°C to inactivate Quantiscript Reverse Transcriptase. Samples can be stored at –20°C for long-term use.

Quantitative real-time PCR was then performed on a LightCycler device using a LightCycler FastStart DNA Master PLUS SYBR Green I Kit (Roche Molecular Biochemicals, Mannheim, Germany), according to the manufacturer's instructions. The total amount of a PCR reaction was 20 µL and composed of 4 µL Master Mix (Roche), 0,25 µL for each primer (10pmol), 2 µL cDNA and 13.5 µL nuclease-free water. The PCR started with an initial denaturation step at 95 °C for 10 min, followed by a total of 45 quantification cycles, consisting of denaturation at 95 °C for 10 s, annealing at primer dependent temperatures for 10 s, and extension at 72 °C for 25 s. The temperature transition rates were set to 20 °C/s in all steps. Following the quantification, DNA melting curves analysis of the products was conducted from 65 °C to 95 °C with an elevated gradient of 0.1 °C/s and continuous monitoring of fluorescence to detect any nonspecific amplification. The majority of the specific primers used for these analyses were designed using Primer Premier 6.0 software (PREMIER Biosoft International, Palo Alto, CA, USA); however, several primer sets were obtained from previous studies (Table S1). Annealing temperatures of the designed primers were calculated using Primer Premier 6.0 software and Tm calculator of the pDRAW32 DNA analysis software. Along with the calculated annealing temperatures, below and above temperature values were assessed and the efficiencies of the primers were compared and optimum annealing temperatures were determined.

All exposed and control samples were analyzed in triplicate, and the averages of these results were used for further evaluation. Fold changes were calculated according to the ΔΔCt method, as described by Livak and Schmittgen (2001). Briefly, the formulas used were as below:

$\Delta C_{T(sample)} = C_{T(sample)} - C_{T(reference)}$

$\Delta C_{T(control)} = C_{T(control)} - C_{T(reference)}$

$\Delta\Delta C_T = \Delta C_{T(sample)} - \Delta C_{T(control)}$

Expression ratio = $2^{-\Delta\Delta CT}$ (2.1)

C_T was the threshold cycle, which demonstrated the fractional cycle number that the amplified target reaches a fixes threshold. ΔC_T was the cycle difference between target and reference. Differences in gene expression levels were calculated after CCW12 normalization relative to the control.

3. RESULTS AND DISCUSSION

3.1. Inhibition of *S. cerevisiae* BY4742 growth upon exposure to BPA and NP

The transcription profiles of *S. cerevisiae* BY4742 were examined after exposure to low and high inhibition concentrations of BPA and NP (resulting in <6% and >70% inhibition in cell number for BPA, and <15% and >65% inhibition in cell number for NP). For these analyses, yeast cultures were treated with BPA (in ethanol) for 180 min beginning at mid-exponential phase (i.e., OD_{600} = 0.8 ± 0.05). On the other hand, the cultures were treated with NP (in ethanol) for 120 and 180 min beginning at mid-exponential phase (i.e., OD_{600} = 0.8 ± 0.05). The exposure period was based on the results of previous studies showing that drug-specific changes in yeast gene expression typically appear a few hours after treatment, although the certain time and magnitude of the observed changes are dependent on the genes and stress conditions (Gil et al. 2011; Gasch and Werner-Washburne 2002).

To determine the appropriate concentrations of BPA for use in the microarray analysis, we exposed yeast cells to various BPA concentrations (1, 5, 25, 50, 75, 100, 120, 140, 160, 200, 250, and 300 mg/L BPA) and measured cell viability by methylene blue staining. Although this method was used to determine the inhibition rates, it also particularly aided to determine the lethal concentration of the BPA. Under the microscope, live cells remained unstained while dead cells were stained blue (Figure 3.1).

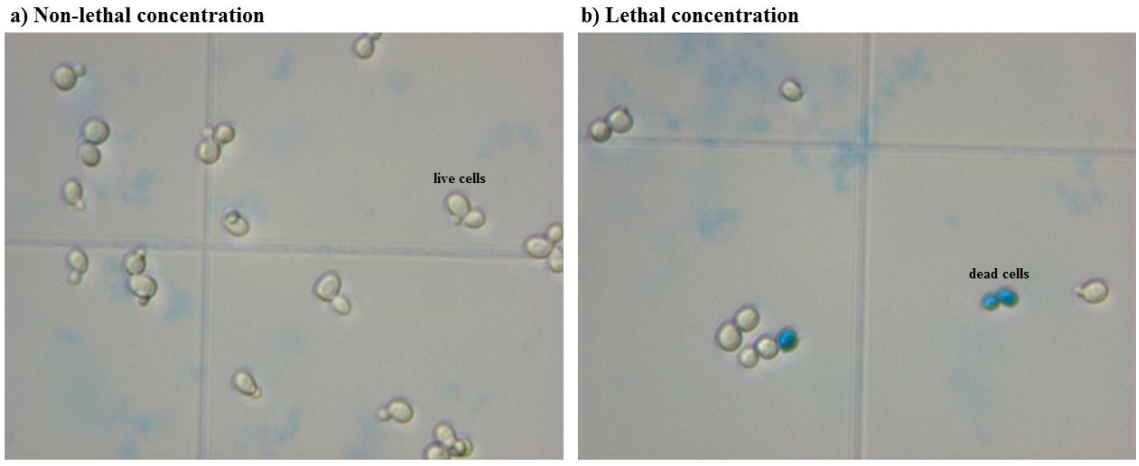


Figure 3.1 Methylene blue staining of yeast cells showing live and dead cells

No effects on growth kinetics or cell viability were observed after exposure to up to 50 mg/L BPA. In contrast, growth inhibition became apparent at this concentration, while cell death occurred at concentrations greater than 300 mg/L BPA. Therefore, 50 mg/L BPA was established as an appropriate low inhibition concentrations (i.e., a concentration that has a small effect on cell number), as it inhibited cell growth at a rate of less than 6% in cell number (5.2% for BPA). Meanwhile, 300 mg/L BPA, which inhibited cell growth at a rate of 71.5% in cell number, was chosen as the high inhibition concentration. Table 3.1 represents the inhibition rates of different BPA concentrations after 3 h exposure. Finally, the growth curve was constructed for the determined concentrations by measuring optical density at 600 nm (Figure 3.2).

Table 3.1 Inhibition rate and cell viability values of different BPA concentrations on the *S. cerevisiae* upon exposure for 3h

Concentration of BPA (mg/L)	**Inhibition rate in cell number (%)**	**Cell viability (%)**
1	not observed	100
5	not observed	100
50	5.2±1.1	94.8±1.1
75	6.2±3.5	93.8±3.5
160	8.3±4.2	91.7±4.2
250	24.8±3.4	75.2±3.4
300	71.5±2.1	28.5±2.1

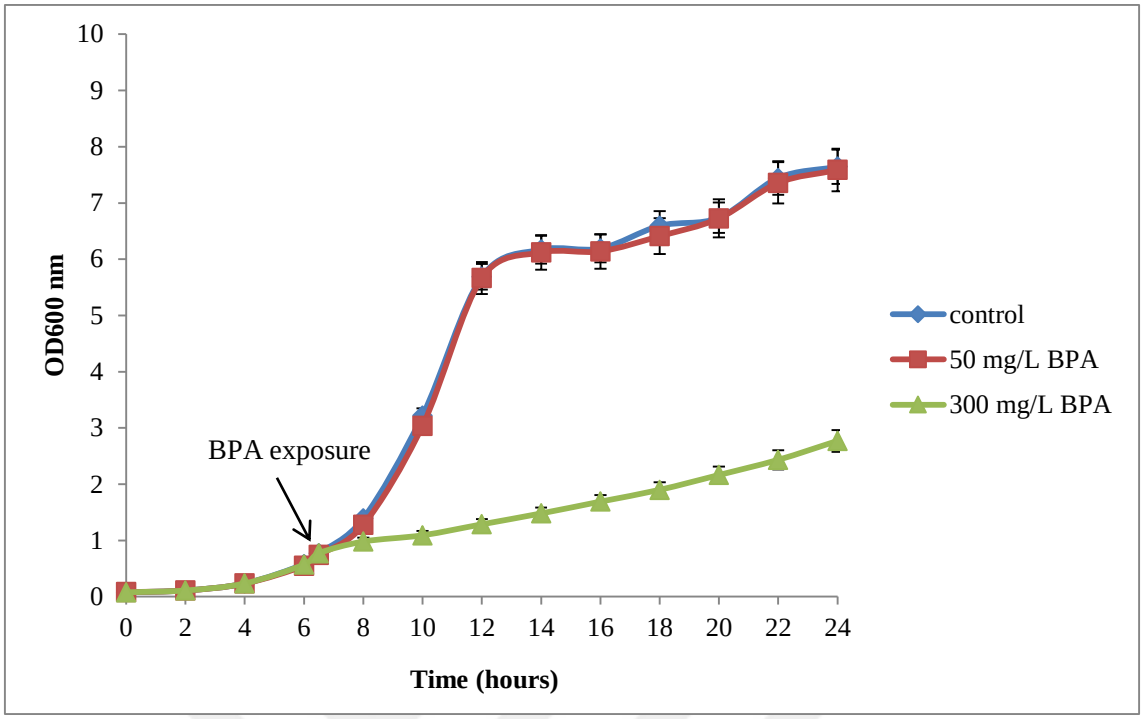


Figure 3.2 Growth curve of *S. cerevisiae* strain BY4742 in the presence or absence of bisphenol A

On the other hand, to determine the appropriate concentrations of NP for use in the microarray analysis, we also exposed yeast cells to various NP concentrations (1, 3, 5, 7.5, 10, and 20 mg/L NP) and measured cell viability by methylene blue staining. The results showed that growth inhibition became apparent at 1 mg/L NP, while cell death occurred at concentrations greater than 5 mg/L NP. Therefore, 1 mg/L NP was established as an appropriate low inhibition concentrations (i.e., a concentration that has a small effect on cell number), as it inhibited cell growth at a rate of less than 15% in cell number (1.4% after 2 h and 11.5% after 3h). Meanwhile, 5 mg/L NP was chosen as the high inhibition concentration, because it inhibited cell growth at a rate of 54.5% in cell number after 2h exposure and 68.4% after 3h exposure (Table 3.2). Following this, the growth curve was constructed for the determined concentrations by measuring optical density at 600 nm (Figure 3.3).

Table 3.2 Inhibition rate and cell viability values of different NP concentrations on the *S. cerevisiae* upon exposure for 2 and 3h

Concentration of NP (mg/L)	Inhibition rate in cell number (%)		Cell viability (%)	
	2 h exposure	3 h exposure	2 h exposure	3 h exposure
1	1.4±3.8	11.5±3.0	98.6±3.8	88.5±3.0
3	47.5±6.5	51.6±5.3	52.5±6.5	48.4±5.3
5	54.5±2.4	68.4±1.2	45.5±2.4	31.6±1.2
7.5	lethal concentration	lethal concentration	-	-
10	lethal concentration	lethal concentration	-	-
20	lethal concentration	lethal concentration	-	-

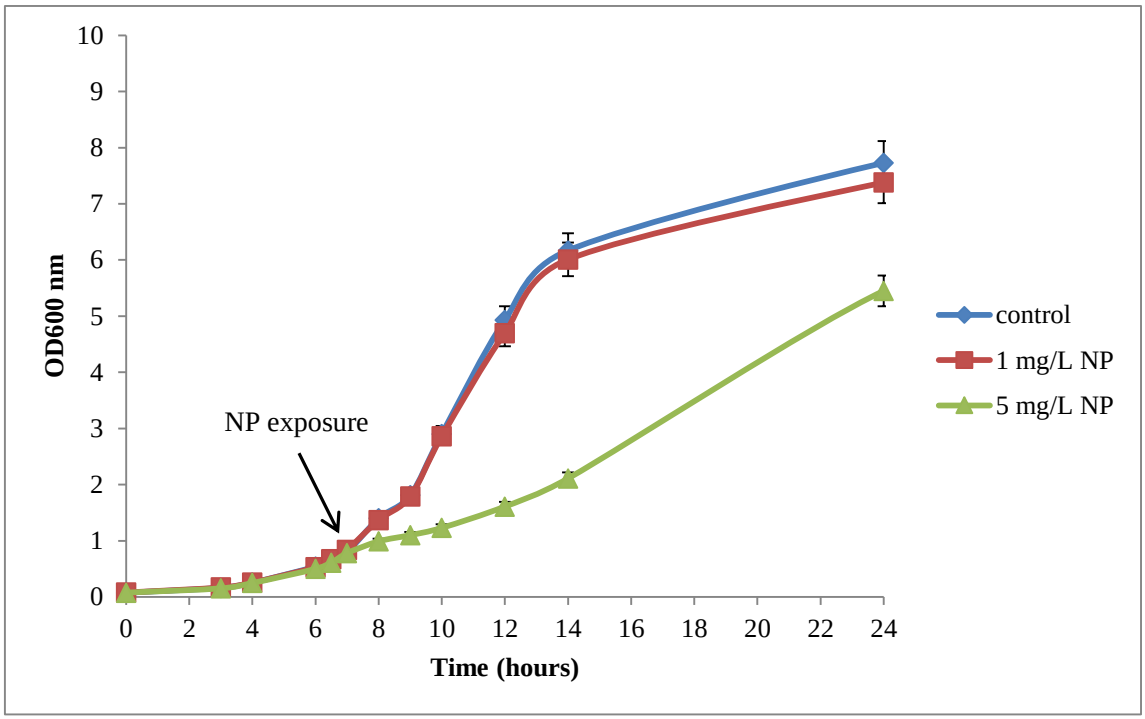


Figure 3.3 Growth curve of *S. cerevisiae* strain BY4742 in the presence or absence of nonylphenol

3.2. The effects of BPA on the gene expression profiles of *S. cerevisiae*

3.2.1. Analysis of the possible toxic effects of exposure to 50 mg/L BPA

Based on the DNA microarray analysis, a total of 185 genes were differentially expressed in yeast exposed to the low inhibition concentration of BPA (50 mg/L) compared with the control. Of these, 81 were downregulated and 104 were upregulated (Figure 3.4). A complete list of these genes and their expression levels can be found in Table S2.

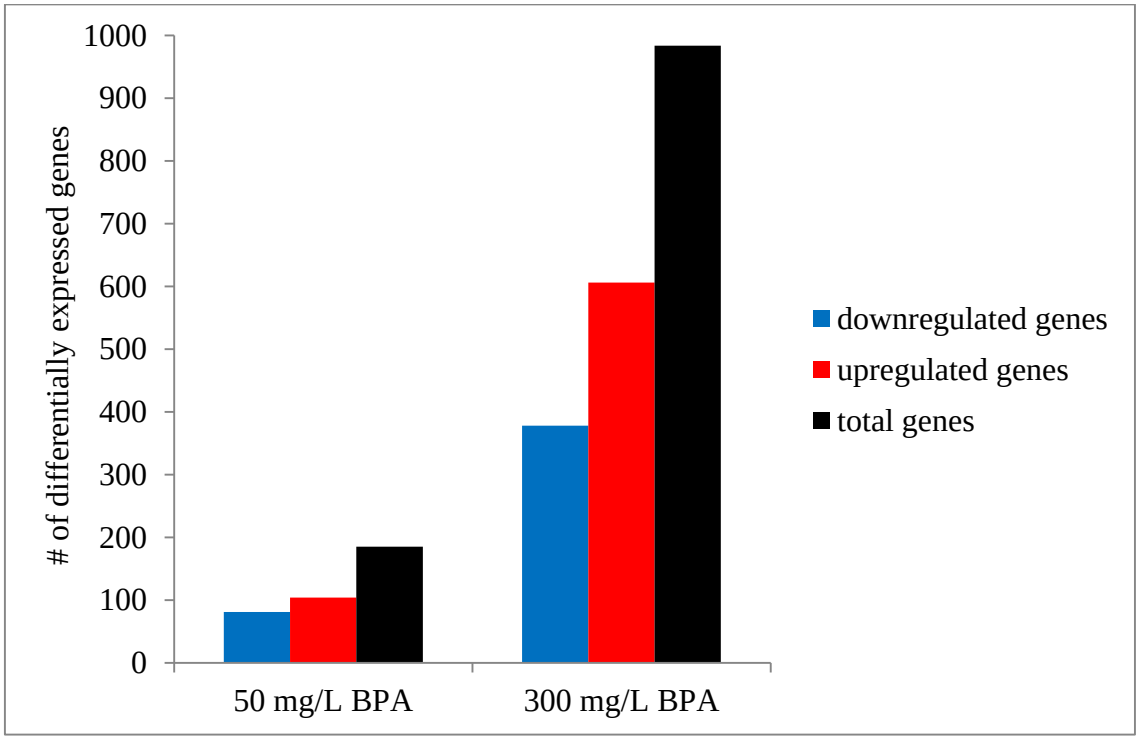


Figure 3.4 Number of differentially expressed genes under bisphenol A (BPA) exposure

Many of the downregulated genes were associated with transport processes (particularly, transmembrane, ion, and carbohydrate transport), mitochondrion organization, metabolic processes such as monocarboxylic acid metabolism, nucleobase-containing small molecule metabolic processes, carbohydrate metabolism, cofactor metabolic processes, cellular amino acid metabolic processes, lipid metabolic processes, and responses to chemicals (Table 3.3).

Table 3.3 Selected biological processes significantly enriched among the genes downregulated in *S. cerevisiae* cells exposed to 50 mg/L bisphenol A (BPA)

GOID	GO term	Frequency	Gene(s)
55085	transmembrane transport	7/81 genes 8.6%	*GIT1*, *TIM22*, *HXT13*, *HXT10*, *PAM18*, *TIM18*, *AQY1*
7005	mitochondrion organization	6/81 genes 7.4%	*TIM22*, *PAM18*, *IMP2*, *TIM18*, *ATG5*, *ICY2*
32787	monocarboxylic acid metabolic process	5/81 genes 6.2%	*ALD5*, *BIO4*, *EEB1*, *CIT3*, *ANT1*
6811	ion transport	5/81 genes 6.2%	*GIT1*, *YKE4*, *MRS4*, *SAM3*, *ANT1*
55086	nucleobase-containing small molecule metabolic process	5/81 genes 6.2%	*FMN1*, *CPD1*, *SAM1*, *APT1*, *ADE12*
5975	carbohydrate metabolic process	4/81 genes 4.9%	*SOR2*, *MNT2*, *FBP1*, *MNT4*
51186	cofactor metabolic process	4/81 genes 4.9%	*FMN1*, *SAM1*, *BIO4*, *COQ10*
6520	cellular amino acid metabolic process	4/81 genes 4.9%	*ARO10*, *ADH4*, *PDC6*, *SAM1*
6629	lipid metabolic process	4/81 genes 4.9%	*SCS3*, *EEB1*, *CIT3*, *ANT1*
42221	response to chemical	3/81 genes 3.7%	*MXR1*, *CUP2*, *TIM18*
8643	carbohydrate transport	3/81 genes 3.7%	*HXT13*, *HXT10*, *HXT2*

3.2.1.1. BPA inhibits the expression of genes encoding sugar and ion transporters and genes involved in sugar metabolism

Among the genes downregulated in response to 50 mg/L BPA were three hexose transporters (*HXT2*, *HXT10*, and *HXT13*), which have been shown to be induced by low levels of glucose and repressed by high levels of glucose (Özcan and Johnston 1999).

We speculate that there would still be sufficient glucose for the growth yeast cells exposed to BPA, as growth inhibition might alter the glucose consumption rate. In addition, five genes (*GIT1*, *YKE4*, *MRS4*, *SAM3*, and *ANT1*) associated with ion transport were also downregulated in the 50 mg/L BPA population. Of these, *GIT1* encodes a plasma membrane permease that mediates the uptake of glycerophosphoinositol and glycerophosphocholine as sources of inositol and phosphate (Patton-Vogt and Henry 1998). Meanwhile, *YKE4* encodes a zinc transporter that localizes to the endoplasmic reticulum and balances zinc levels between the cytosol and the secretory pathway (Kumánovics et al. 2006), and *MRS4* encodes an iron transporter of the mitochondrial carrier family that mediates the transport of Fe^{2+} across the inner mitochondrial membrane (Froschauer et al. 2009). Lastly, *ANT1* encodes a peroxisomal adenine nucleotide transporter involved in beta-oxidation of medium-chain fatty acids and is required for peroxisome proliferation (Palmieri et al. 2001), while *SAM3*, which also functions in ion transport, encodes a high-affinity *S*-adenosylmethionine permease and is required for the utilization of *S*-adenosylmethionine as a sulfur source (Rouillon et al. 1999).

Four genes involved in carbohydrate metabolism, *SOR2*, *FBP1*, *MNT2*, and *MNT4*, were significantly downregulated upon exposure to low inhibition level of BPA. *SOR2* encodes a protein of unknown function that is computationally predicted to be involved in hexose metabolism based on its interaction partners (Samanta and Liang 2003). *FBP1* (fructose-1,6-biphosphatase) encodes a key regulatory enzyme involved in the gluconeogenesis pathway that is required for glucose metabolism (Alibhoy et al. 2012). *MNT2* encodes a mannosyltransferase involved in the addition of the 4th and 5th mannose residues to *O*-linked glycans, while *MNT4* encodes a putative alpha-1,3-mannosyltransferase that is not required for protein *O*-glycosylation (Romero et al. 1999).

3.2.1.2. Exposure to BPA may negatively affect mitochondrial biogenesis

Mitochondrial membrane organization also appeared to be significantly affected by BPA exposure, as evidenced by the downregulation of *TIM18*, *TIM22*, *PAM18*, and *IMP2*. *TIM18* and *TIM22* encode essential components of the TIM22 complex, which mediates the insertion of large hydrophobic proteins, such as transporters, into the

mitochondrial inner membrane (Koehler et al. 2000). Similarly, *PAM18* and *IMP2* encode subunits of the TIM23 and peptidase complexes, respectively, which are essential components of the mitochondrial inner membrane (Truscott et al. 2003; Luo et al. 2006). Together, the observed transcriptional repression of components of these mitochondrial inner membrane complexes suggests that BPA affects mitochondrial biogenesis.

3.2.1.3. Exposure to BPA results in downregulation of genes involved in nucleobase-containing molecules

With respect to nucleobase-containing small molecule metabolic processes, exposure to the low inhibition concentration of BPA resulted in downregulation of *SAM1*, *FMN1*, *CPD1*, *APT1*, and *ADE12*. The *SAM1* gene product is an *S*-adenosylmethionine synthetase that catalyzes the biosynthesis of AdoMet, which is involved in the methylation of proteins, RNAs, and lipids, and in the biosynthesis of biotin and polyamines from methionine and ATP (Kodaki et al. 2003). *FMN1*, a riboflavin kinase that produces riboflavin monophosphate, is a necessary cofactor for many enzymes and is found in the mitochondrial inner membrane (Santos et al. 2000). As such, the observed repression of this gene supports our hypothesis that BPA affects mitochondrial biogenesis. *CPD1* encodes a cyclic nucleotide phosphodiesterase, which may play a role in tRNA splicing (Nasr and Filipowicz 2000). Finally, *APT1* encodes the yeast adenine phosphoribosyltransferase (APRT), which catalyzes the condensation of adenine and 5-phosphoribosylpyrophosphate to yield adenosine monophosphate (AMP), and is also involved in the salvage pathway of purine nucleotide biosynthesis (Alfonzo et al. 1995), while *ADE12* encodes an adenylosuccinate synthase that catalyzes the first step in the synthesis of AMP from inosine 5′ monophosphate during purine nucleotide biosynthesis (Lipps and Krauss 1999). The downregulation of genes associated with AMP synthesis suggests that BPA may influence purine nucleotide biosynthesis.

Meanwhile, the majority of the genes that were upregulated in response to exposure to 50 mg/L BPA were associated with transcription from the RNA polymerase II promoter, mitosis and associated processes, responses to chemical and DNA damage, or DNA repair (Table 3.4).

Table 3.4 Selected biological processes significantly enriched among the genes upregulated in *S. cerevisiae* cells exposed to 50 mg/L bisphenol A (BPA)

GOID	GO term	Frequency	Gene(s)
6366	transcription from RNA polymerase II promoter	17/104 genes 16.3%	*TAF2*, *MBP1*, *BUR6*, *ITC1*, *NUT1*, *TFG1*, *MGA2*, *GAL80*, *RCO1*, *HOT1*, *SPT21*, *DCP2*, *TOP1*, *ISW2*, *NDD1*, *GCR1*, *HDA3*
278	mitotic cell cycle	16/104 genes 15.4%	*KCC4*, *MRC1*, *MPS1*, *MBP1*, *CIN8*, *MAD1*, *KEL2*, *KEL1*, *IRR1*, *BIR1*, *HSL1*, *TOP2*, *CNM67*, *TOP1*, *NDD1*, *AIM44*
48285	organelle fission	15/104 genes 14.4%	*MRC1*, *MPS1*, *ECM11*, *CIN8*, *MAD1*, *IME4*, *KEL2*, *KEL1*, *IRR1*, *HOS4*, *BIR1*, *SET3*, *TOP2*, *PDR16*, *TOP1*
6325	chromatin organization	14/104 genes 13.5%	*BDF2*, *NGG1*, *ITC1*, *RAD54*, *HOS4*, *RAD26*, *SET3*, *RCO1*, *TOP2*, *TOP1*, *ULS1*, *ISW2*, *GCR1*, *HDA3*
51726	regulation of cell cycle	12/104 genes 11.5%	*KCC4*, *MRC1*, *MPS1*, *MAD1*, *KEL2*, *KEL1*, *HOS4*, *BIR1*, *HSL1*, *SET3*, *TOP2*, *PDR16*
42221	response to chemical	11/104 genes 10.6%	*AFR1*, *VPS64*, *ITC1*, *CUP1-1*, *MGA2*, *FAR10*, *FUS2*, *PDR16*, *PDR5*, *ISW2*, *GCR1*
7010	cytoskeleton organization	10/104 genes 9.6%	*KCC4*, *MPS1*, *RGA2*, *CIN8*, *KEL2*, *MYO1*, *KEL1*, *BIR1*, *KAR1*, *CNM67*
33043	regulation of organelle organization	9/104 genes 8.7%	*MPS1*, *BDF2*, *MAD1*, *KEL2*, *KEL1*, *HOS4*, *BIR1*, *SET3*, *PDR16*

Table 3.4 continued

6974	cellular response to DNA damage stimulus	8/104 genes 7.7%	*MRC1*, *POL4*, *RTT103*, *RAD34*, *RAD54*, *RAD26*, *ULS1*, *REV3*
7059	chromosome segregation	8/104 genes 7.7%	*MRC1*, *MPS1*, *CIN8*, *MAD1*, *IRR1*, *BIR1*, *TOP1*, *HDA3*
6281	DNA repair	7/104 genes 6.7%	*MRC1*, *POL4*, *RAD34*, *RAD54*, *RAD26*, *ULS1*, *REV3*

3.2.1.4. BPA may promote RNA polymerase II-mediated transcription

Basal transcription of most protein-coding genes, which is the major regulatory step in differential gene expression and cell growth, requires the activity of RNA polymerase II as well as general transcription factors, including TFIID and TFIIF (Prelich 1997). TFIID is a complex composed of TATA-binding protein (TBP; Spt15p), which is highly conserved among all eukaryotes, and several TBP-associated factors (TAFs). Meanwhile, TFIIF stabilizes RNA polymerase II when it contacts *TBP* (Hahn and Young 2011). We detected upregulation of two important subunits of TFIID and TFIIF upon exposure to BPA. Specifically, we detected enhanced transcription of *TAF2* and *TFG1*, which encode a TFIID subunit involved in RNA polymerase II transcription initiation and the largest subunit of TFIIF, which is essential for transcription initiation and elongation of RNA polymerase II, respectively (Sun and Hampsey 1995; Tora 2002). Moreover, three additional genes involved in transcription were induced under these conditions: *BDF2*, *NUT1*, and *BUR6*. *BDF2* encodes a protein involved in transcription initiation that is associated with the basal transcription factor TFIID. BDF2 also catalyzes histone acetylation, resulting in the recruitment of bromodomain-containing proteins (Fu et al. 2013). Meanwhile, *NUT1* encodes a component of the RNA polymerase II mediator complex that is required for transcriptional activation (Gustafsson et al. 1998), and *BUR6* encodes a subunit of a heterodimeric NC2 transcription regulator complex that stimulates activate transcription by binding to *TBP* (Cang and Prelich 2002). The increased mRNA expression of these genes suggests that yeast cells respond to BPA and adapt to new conditions by increasing RNA polymerase

II-mediated transcription as well as by promoting histone acetylation, which is necessary for protecting the genome and modulating gene expression via packaging of the DNA into chromatin.

3.2.1.5. Exposure to 50 mg/L BPA results in upregulation of genes involved in DNA repair

Upon exposure of *S. cerevisiae* to 50 mg/L BPA, we detected significantly increased expression of *RAD26*, *RAD34*, *RAD54*, *REV3*, *POL4*, and *ULS1*, each of which contribute to DNA repair and/or the cellular response to DNA damage. *RAD26* encodes a protein involved in transcription-coupled repair that also forms a complex with the RNA polymerase II degradation factor Def1p, suggesting an interaction between the ubiquitylation of RNA polymerase II and DNA damage (Malik and Bhaumik 2012). *RAD34* encodes a protein that functions in nucleotide excision repair, while *RAD54* is a damage-inducible gene that has been shown to be induced by a diverse array of DNA-damaging agents, and is involved in the recombination-mediated repair of double-stranded DNA breaks (Cole and Mortimer 1989). REV3 is involved in the recovery of mutations caused by DNA damage and double-strand break repair within the nuclear genome (Morrison et al. 1989). *POL4* encodes DNA polymerase IV, which undergoes pair-wise interactions with Dnl4p-Lif1p and Rad27p to mediate the repair of DNA double-strand breaks via non-homologous end joining (Tseng and Tomkinson 2004). Finally, *ULS1* encodes a Swi2/Snf2-related translocase that functions at telomeres to translocate and ubiquitinylate poly-sumoylated Rap1p for proteosomal degradation, and is required for S phase progression in the presence of DNA damage (Cal-Bakowska et al. 2011). Several previous studies have demonstrated that certain compounds, such as *p*-anisaldehyde and vanillin, effectively induce various DNA repair genes. Indeed, it was proposed that the antimutagenic activity of vanillin promotes recombination and rejoining of DNA at homologous sites of damaged cells (Tamai et al. 1992; Yu et al. 2010). In addition, the protein-small molecule complex neocarzinostatin (NCS) promotes the expression of several DNA damage and repair genes in *S. cerevisiae* (Schaus et al. 2001). Based on our current results and those of previous studies, we postulate that BPA induces DNA damage and double-strand breaks, and that yeast cells respond to these effects by inducing DNA repair-related genes.

3.2.1.6. Exposure to 50 mg/L BPA results in upregulation of genes involved in cell cycle progression and replication

Several genes involved in nuclear division and cell cycle progression, including *NDD1*, *MBP1*, and *MRC1* were also induced upon exposure to low inhibition level of BPA. These genes are known to be required for maintenance of genome integrity by detecting DNA damage, encoding proteins necessary for DNA repair, and arresting cells for repair. Specifically, *NDD1* encodes a transcriptional activator essential for nuclear division and for the expression of a set of late-S-phase-specific genes (Loy et al. 1999). *MBP1* encodes a transcription factor involved in the regulation of cell cycle progression from G1 to S phase, and in the formation of the MBF (Mlul cell cycle box-Binding Factor) complex with Swi6p. The MBF complex in turn acts as a transcription factor that regulates the expression of several genes involved in the cell cycle, and in DNA synthesis and repair (Koch et al. 1993; Yu et al. 2010). Notably, Yu *et al*. (2010) previously demonstrated that *MBP1* is repressed upon exposure to *p*-anisaldehyde, which contrasts with our observations for BPA. In another study, a delay in the replicative portion of the cell cycle owing to a loss of Mbp1p resulted in an increase in modal cell volume and in the number of budded cells (Bean et al. 2005). Meanwhile, *MRC1* encodes an S-phase checkpoint protein required for transmission of the DNA replication arrest signal to downstream effectors via the activation of Rad53 kinase in response to replication stress (Xu et al. 2004). Schaus *et al*. (2001) demonstrated that the NCS of yeast increases the transcript levels of the cell cycle genes *MEC1* and *RAD9*, which encode checkpoint proteins that promote cell cycle arrest in response to DNA damage and are required for the repair of double-strand breaks. Taken together, our findings demonstrate that low inhibition level of BPA promote the expression of genes related to DNA repair, cellular responses to DNA damage, and cell cycle progression and arrest, suggesting that this compound has an effect on the cell cycle.

Biochemical and genetic analyses have indicated that proper spindle function requires various proteins, such as microtubules, kinetochores, spindle poles, microtubule-based motor proteins, and multiple regulatory enzymes (Geiser et al. 1997). We observed the upregulation of several genes that are essential for spindle function in *S. cerevisiae* exposed to 50 mg/L BPA. *CNM67* encodes a protein that localizes to the

microtubule organization center, the spindle pole body (SPB), and is required for SPB and mitotic nuclear migration. The deletion of *CNM67* causes spindle mis-orientation and impaired nuclear migration, leading to the generation of bi- and multinucleated cells. Furthermore, this protein is required for formation of proper SPB outer plaque structures, which nucleate astral (cytoplasmic) microtubules (Brachat et al. 1998). *MPS1* encodes a major protein kinase required for SPB duplication and for spindle checkpoint function. In cells with defects in mitotic spindle assembly, the spindle checkpoint postpones the onset of anaphase. Mps1p phosphorylates the checkpoint protein Mad1p, and overexpression of *MPS1* arrests cells in mitosis (Weiss and Winey 1996). In a recent study, Kamthan *et al*. (2014) observed that *mps1*-deficient *Candida albicans* mutants exhibit a dramatic loss of viability in the presence of an anti-microtubule drug, suggesting a role for *MPS1* in the spindle checkpoint. Meanwhile, the expression levels of *MAD1* encoding a protein involved in the spindle-assembly checkpoint that is phosphorylated by Mps1p, was also upregulated in response to low inhibition concentration of BPA. A homolog of Mad1p, *MAD1L1*, functions in the spindle checkpoint in humans (Jin et al. 1998). *CIN8* encodes a kinesin motor protein involved in mitotic spindle assembly and chromosome segregation that is also required for the maintenance of spindle bipolarity following assembly and for spindle-elongating force during anaphase (Gheber et al. 1999). *BIR1* encodes a subunit of chromosomal passenger complex, which is an essential regulator of chromosome segregation, spindle checkpoints, and cytokinesis. Members of the chromosomal passenger complex are conserved from yeast to humans, and the Bir1p subunit is required for chromosome bi-orientation and activation of the spindle assembly checkpoint upon reduced sister kinetochore tension. This protein also contains a motif (domain) that is typically found in inhibitors of apoptosis proteins (Ruchaud et al. 2007).

Septins are required for cytokinesis and various processes, including the organization of cell surfaces, and are conserved among eukaryotes. Indeed, mutations in septin and treatment with anti-septin agents result in inhibition of cytokinesis in budding yeast and mammalian cells (Okuzaki and Nojima 2001). *KCC4* and *HSL1* are homologous genes that encode protein kinases of the bud neck that are involved in the regulation of morphogenesis and septin checkpoints. Specifically, these proteins associate with septin proteins (Okuzaki and Nojima 2001) and negatively regulate

Swe1p, which relays morphogenetic signals to cell cycle factors by delaying the onset of mitosis via the phosphorylation and inactivation of the cyclin-dependent kinase Cdc28p (Okuzaki et al. 2003). *RGA2* encodes a GTPase-activating protein that is implicated in the control of septin organization, pheromone response, and haploid invasive growth, and is regulated by Cdc28p and Pho85p (Sopko et al. 2007).

Lastly, we detected increased expression of the topoisomerases *TOP1* and *TOP2* upon exposure of *S. cerevisiae* to 50 mg/L BPA. Topoisomerases catalyze the conversion between topological states of DNA by breaking and rejoining DNA strands. This activity is necessary for various cellular processes, including replication, transcription, recombination, and chromosome condensation (Berger 1998).

In summary, these data demonstrate that BPA affects processes such as spindle function, DNA repair mechanisms, nuclear division, chromosomal segregation, and cytokinesis, indicating that BPA exposure triggers mechanisms associated with cell cycle progression and DNA repair in yeast.

3.2.1.7. Exposure to 50 mg/L BPA results in increased expression of genes involved in yeast cell fusion

In yeast, haploid cells respond to the peptide pheromone secreted by cells of the opposite mating type and cell fusion is triggered. The pheromones bind to a seven-transmembrane receptor, which in turn stimulates a signal transduction cascade and results in cell cycle arrest (Philips and Herskowitz 1998). In our study, we detected changes in several genes related to cell fusion and mitotic exit. *KEL1* and *KEL2* encode proteins that form a complex with Bud14p, which regulates formin (Bnr1p) to affect actin assembly, cytokinesis, and polarized growth. Kel1 and Kel2 function in this complex to negatively regulate mitotic exit (Philips and Herskowitz 1998; Gould et al. 2014). Philips and Herskowitz (1998) demonstrated that overexpression of *KEL1* and *KEL2* is sufficient to suppress defects in cell fusion in certain mutant cells. Lastly, *IRR1* encodes a subunit of the yeast cohesion complex required for sister chromatid cohesion during mitosis and meiosis, and is associated with centromeres prior to metaphase (Cena et al. 2013). Cena *et al*. (2013) found that mutations in this gene are lethal in haploid cells, and observed a role for the gene in the regulation of transcription in a gene expression analysis of heterozygous diploid yeast cells.

3.2.1.8. BPA promotes the expression of drug resistance genes

The pleiotropic drug resistance (PDR) network involved in multidrug resistance (MDR) is constitutively regulated by the transcription factors Pdr1p and Pdr3p in *S. cerevisiae* (Bauer et al. 1999). Two PDR genes, *PDR5* and *PDR16*, were induced upon BPA exposure. *PDR5* encodes the plasma membrane ATP-binding cassette (ABC) transporter Pdr5p, which is positively regulated by Pdr1p and Pdr3p. Pdr5p efflux pump activity mediates resistance to various xenobiotic compounds such as mutagens, fungicides, steroids, and anticancer drugs (Bauer et al. 1999). The ABC superfamily of proteins is highly conserved from bacteria to humans (Bauer et al. 1999), and overexpression of the human ABC transporter ABCB1/MDR1 is involved in tumor resistance to drug therapy, while deficiencies in this transporter are associated with various human diseases (Decottignies and Goffeau 1997). Meanwhile, *PDR16* encodes a phosphatidylinositol transfer protein that is controlled by the MDR regulator Pdr1p and that controls the levels of various lipids. Increased Pdr16p expression was also detected in response to DNA replication stress (van den Hazel et al. 1999).

3.2.2. Analysis of the possible toxic effects of exposure to 300 mg/L BPA

A total of 984 genes were differentially expressed by at least 1.5-fold (corresponding to a 50% modification in gene expression) in *S. cerevisiae* cells exposed to 300 mg/L BPA compared to the control cells. Of these, 378 were downregulated and 606 were upregulated (Figure 3.4). A complete list of the differentially expressed genes in response to 300 mg/L BPA exposure and their expression levels can be found in Table S3. As shown in Table 3.5, a significant proportion of the downregulated genes were involved in metabolic processes, particularly nucleobase-containing small molecule metabolism, carbohydrate metabolism, lipid metabolism, monocarboxylic acid metabolism, and cofactor metabolic processes. In addition, numerous genes were associated with mitochondrion organization and associated processes, responses to chemicals, and ion transport.

Table 3.5 Selected biological processes significantly enriched among the genes downregulated in *S. cerevisiae* cells exposed to 300 mg/L bisphenol A (BPA)

GOID	GO term	Frequency	Gene(s)
55086	nucleobase-containing small molecule metabolic process	51/378 genes 13.5%	*BNA4*, *ATP3*, *GLK1*, *ATP16*, *GPD1*, *COX9*, *QRI1*, *SDH4*, *ATP5*, *HNT2*, *QCR7*, *RIP1*, *CYC7*, *BNA6*, *HXK1*, *PNC1*, *COX4*, *SOL4*, *ENO1*, *QCR10*, *COX6*, *COX5B*, *RNR2*, *TDH1*, *QCR8*, *BNA1*, *CYC1*, *BNA2*, *URA8*, *ATP2*, *ATP7*, *UGP1*, *SDH3*, *SDH1*, *SDH2*, *TAL1*, *ADE13*, *COX8*, *ATP18*, *NDI1*, *PGM2*, *ADE17*, *COX7*, *PRM15*, *COX5A*, *ADE12*, *CYT1*, *CDC21*, *ADE2*, *ISN1*, *QCR2*
7005	mitochondrion organization	47/378 genes 12.4%	*MBA1*, *MRPS5*, *MRPL32*, *HCM1*, *MRPL1*, *KGD2*, *RSM24*, *MRPL35*, *SDH6*, *QCR7*, *COX13*, *MSP1*, *SHY1*, *MRPS35*, *AIM17*, *RSM25*, *COA1*, *MEF2*, *ATP12*, *ILM1*, *SDH3*, *MST1*, *MRPL13*, *MIC60*, *LMO1*, *MEF1*, *MSS51*, *MRPL15*, *ATG33*, *ATG17*, *ATP18*, *RPM2*, *SAM37*, *ABF2*, *MTF1*, *SAM50*, *ATG4*, *MRPL3*, *MRPL24*, *ATP11*, *ATG3*, *RCF2*, *MSE1*, *TUF1*, *COA2*, *CBP3*, *MRPL17*

Table 3.5 continued

6091	generation of precursor metabolites and energy	41/378 genes 10.8%	*PSK1*, *COR1*, *ETR1*, *GLK1*, *COX9*, *KGD2*, *SDH4*, *QCR7*, *GLC3*, *RIP1*, *CYC7*, *RGI1*, *GSY1*, *HXK1*, *COX4*, *COX13*, *ENO1*, *QCR10*, *COX6*, *MAM33*, *COX5B*, *KGD1*, *TDH1*, *QCR8*, *CYC1*, *UGP1*, *MDH1*, *SDH3*, *SDH1*, *SDH2*, *GSY2*, *COX8*, *NDI1*, *PGM2*, *COX7*, *COX5A*, *CIT1*, *CYT1*, *PHO85*, *GPH1*, *QCR2*
5975	carbohydrate metabolic process	32/378 genes 8.5%	*PSK1*, *TPS1*, *ARA1*, *GLK1*, *YPR1*, *GLC3*, *UBC8*, *GPP2*, *GSY1*, *HXK1*, *OCH1*, *ALG2*, *GSC2*, *XKS1*, *ENO1*, *MAL13*, *GRE3*, *FYV10*, *TDH1*, *MNN5*, *UGP1*, *GSY2*, *TSL1*, *YMR099C*, *PGM2*, *MLS1*, *ALG9*, *GAS5*, *MDH2*, *KTR1*, *PHO85*, *GPH1*
42221	response to chemical	28/378 genes 7.4%	*FUS3*, *PRX1*, *GRX7*, *FIG1*, *ZTA1*, *TPS1*, *GRX1*, *KAR4*, *HCM1*, *KIN82*, *YPR1*, *ZNF1*, *FAR7*, *STF2*, *SOD2*, *GRE3*, *IMP2'*, *HYR1*, *SAG1*, *MSN4*, *MCR1*, *STE3*, *CCP1*, *CSI1*, *GAD1*, *BXI1*, *AGA1*, *SVS1*

Table 3.5 continued

45333	cellular respiration	28/378 genes 7.4%	*COR1*, *ETR1*, *COX9*, *KGD2*, *SDH4*, *QCR7*, *RIP1*, *CYC7*, *COX4*, *COX13*, *QCR10*, *COX6*, *MAM33*, *COX5B*, *KGD1*, *QCR8*, *CYC1*, *MDH1*, *SDH3*, *SDH1*, *SDH2*, *COX8*, *NDI1*, *COX7*, *COX5A*, *CIT1*, *CYT1*, *QCR2*
6629	lipid metabolic process	27/378 genes 7.1%	*SCS22*, *ETR1*, *FAT1*, *YPC1*, *TSC13*, *TGL2*, *HST4*, *DPP1*, *LPP1*, *ERG28*, *ERG26*, *ALG2*, *AYR1*, *GWT1*, *ERG20*, *TES1*, *URA8*, *MCR1*, *GPT2*, *CKI1*, *ERG13*, *YMR210W*, *SCS7*, *GPI12*, *TGL5*, *YDC1*, *EEB1*
70271	protein complex biogenesis	26/378 genes 6.9%	*SCO1*, *MBA1*, *TMA17*, *UBC13*, *SDH6*, *QCR7*, *GAL83*, *MMS2*, *HUL5*, *TWF1*, *SHY1*, *COA1*, *ATP12*, *RAV1*, *CAP1*, *PEP3*, *MSS51*, *ATP18*, *SAM37*, *AIP1*, *SAM50*, *ATP11*, *RCF2*, *COA2*, *CBP3*, *COX13*
51186	cofactor metabolic process	24/378 genes 6.3%	*BNA4*, *COQ1*, *GLK1*, *GPD1*, *COQ4*, *COX15*, *BNA6*, *HXK1*, *PNC1*, *HEM2*, *SOL4*, *ENO1*, *COQ6*, *TDH1*, *BNA1*, *BNA2*, *COQ9*, *TAL1*, *NDI1*, *CIT1*, *COQ2*, *CAT5*, *HEM15*, *FAA1*

Table 3.5 continued

32543	mitochondrial translation	20/378 genes 5.3%	*MBA1*, *MRPS5*, *MRPL32*, *MRPL1*, *RSM24*, *MRPL35*, *MRPS35*, *RSM25*, *MEF2*, *MST1*, *MRPL13*, *MEF1*, *MSS51*, *MRPL15*, *MRPL3*, *MRPL24*, *MRPL17*, *MSE1*, *TUF1*, *CBP3*
55085	transmembrane transport	17/378 genes 4.5%	*ATP3*, *ERS1*, *ATP16*, *ATP5*, *HXT7*, *PIC2*, *VPS73*, *ATP2*, *ATP7*, *SDH3*, *MIC60*, *ATP18*, *SAM37*, *SAM50*, *SIL1*, *MDH2*, *YBR241C*
6811	ion transport	16/378 genes 4.2%	*SCO1*, *ATP3*, *FAT1*, *ERS1*, *KIN82*, *ATP16*, *ATP5*, *PIC2*, *TPO2*, *ATP2*, *ATP7*, *ATP18*, *SAM37*, *SMF1*, *FAA1*, *OPT2*
32787	monocarboxylic acid metabolic process	15/378 genes 4%	*ETR1*, *FAT1*, *GLK1*, *TSC13*, *DLD2*, *HST4*, *FDC1*, *HXK1*, *ENO1*, *TDH1*, *TES1*, *YMR210W*, *MLS1*, *GOR1*, *EEB1*
6979	response to oxidative stress	14/378 genes 3.7%	*PRX1*, *GRX7*, *ZTA1*, *TPS1*, *GRX1*, *HCM1*, *YPR1*, *SOD2*, *GRE3*, *HYR1*, *MSN4*, *MCR1*, *CCP1*, *GAD1*

3.2.2.1. Exposure to 300 mg/L BPA results in reduced expression of genes involved in oxidative phosphorylation (OXPHOS)

Mitochondria are the main energy (ATP) producers in eukaryotic cells. Several crucial metabolic processes, including OXPHOS, the tricarboxylic acid cycle (TCA), and lipid β-oxidation, occur in mitochondria. Specifically, the OXPHOS system, which includes five enzyme complexes (complex I to complex V) and two electron carriers (quinone-coenzyme Q and cytochrome C), converts substrates produced via glycolysis and β-

oxidation into energy (ATP) (Fernandez-Vizarra et al. 2009). Additionally, mitochondria play an active role in death and survival signaling pathways. In particular, many mitochondrial diseases and serious neurodegenerative diseases, such Parkinson's, Alzheimer's, and Huntington's disease, are linked to mitochondrial defects (Diaz 2010). Several genes associated with the OXPHOS system were downregulated in *S. cerevisiae* in response to exposure to 300 mg/L BPA. Of these, *NDI1* encodes the ubiquinone oxidoreductase NADH that forms complex I in *S. cerevisiae*. Ndi1 is the major entry point for electrons into the electron transport chain. Mammalian complex I consists of 46 subunits, and defects in complex I are associated with various human disorders such as Leber's hereditary disease, optic neuropathy, and cancer (Iwata et al. 2012).

In addition to those involved in complex I, five genes (*SDH1*, *SDH2*, *SDH3*, *SDH4*, and *SDH6*) associated with mitochondrial complex II [i.e., succinate dehydrogenase (SDH)] were downregulated upon exposure to high inhibition level of BPA. Complex II comprises the second entry point of reducing equivalents into the mitochondrial respiratory chain via FADH, which is produced by the conversion of succinate to fumarate in the TCA cycle (Grimm 2013). In humans, complex II subunits function as tumor suppressors, and deficiencies in this complex have been shown to cause certain types of cancer (Kluckova et al. 2013). Among the subunits downregulated in response to BPA, *SDH1* encodes the flavoprotein subunit of SDH, while *SDH2* encodes the iron-sulfur protein subunit that couples the oxidation of succinate to the transfer of electrons to ubiquinone as part of the TCA cycle and the mitochondrial respiratory chain (Oyedotun and Lemire 2004; Kim et al. 2012). *SDH3* encodes the SDH subunit and TIM22 translocase, which functions as the cytochrome b subunit of SDH and is required for mitochondrial inner membrane protein import as part of the TIM22 complex (Gebert et al. 2011). Finally, *SDH4* encodes a membrane anchor subunit of SDH that is similar to human SDH subunit D (Oyedotun and Lemire 2004), and *SDH6* encodes a mitochondrial protein involved in SDH assembly and that plays a role in the maturation of the Sdh2p subunit (Na et al. 2014).

Several genes associated with mitochondrial complex III, also known as ubiquinol cytochrome-c reductase or cytochrome bc1 complex, were repressed in *S. cerevisiae* upon exposure to high inhibition level of BPA. The cytochrome bc1 complex is a highly conserved enzyme of the mitochondrial respiratory chain. In *S. cerevisiae*, this complex

is comprised of three catalytic subunits (Cobp, Rip1p, and Cyt1p) and seven additional subunits (Cor1p, Qcr2p, Qcr6p, Qcr7p, Qcr8p, Qcr9p, and Qcr10p) (Hunte et al. 2003; Benit et al. 2009). Upon exposure to 300 mg/L BPA, we observed reduced expression of *RIP1* and *CYT1*, which encode the catalytic subunits Rip1p and Cyt1p, respectively. Rip1p is a Rieske iron-sulfur protein that is essential for complex III activity, and mediates the transfer of electrons from ubiquinol to cytochrome c1 during respiration (Beckmann et al. 1987). Likewise, Cyt1p, commonly known as cytochrome c1, plays essential roles in electron transfer within the complex and in respiratory growth (Hunte et al. 2003). Furthermore, we detected repression of the following six complex III-associated genes under the high inhibition condition: *QCR2*, *QCR7*, *QCR8*, *QCR10*, *COR1*, and *CBP3*. *CBP3* encodes one of two known proteins that are not components of the complex *per se*, but are essential for the assembly of a functional complex (Kronekova and Rodel 2005), while *COR1*, which is conserved in other eukaryotes, encodes one of the so-called "core" subunits that are essential for the assembly and activity of the cytochrome bc1 complex and for respiratory growth (Gatti and Tzagoloff 1990). *QCR2*, *QCR7*, *QCR8*, and *QCR10* encode subunits that are crucial for the activity of the cytochrome bc1 complex and are conserved across eukaryotes. Various studies have shown that mutations in these subunits severely or completely inhibit the activity of the complex (Crivellone et al. 1988; Lee et al. 2001; Hagerman et al. 2006). Meanwhile, certain mutations in *QCR8* have been shown to negatively affect the activity of complex II, indicating that the Qcr8p subunit may mediate interactions between complex II and III (Bruel et al. 1996).

Mitochondrial respiratory chain complex IV, referred to as cytochrome c oxidase (COX), was also affected by the high inhibition concentration of BPA. The transfer of electrons from cytochrome c to oxygen is catalyzed by COX, which consists of three core subunits encoded by the mitochondrial genome (Cox1p, Cox2p, and Cox3p) and eight additional subunits encoded by nuclear genes (Cox4p, Cox5Ap, Cox5Bp, Cox6p, Cox7p, Cox8p, Cox9p, Cox12p, and Cox13p) (Geier et al. 1995). We found that 13 genes associated with COX were significantly downregulated in response to 300 mg/L BPA. Of these, seven were nuclear genes encoding complex subunits (Cox4p, Cox5A-Bp, Cox6p, Cox7p, Cox8p, Cox9p, and Cox13p), while the remaining six encoded mitochondrial inner membrane proteins (Cox15p, Coa1p, Coa2p, Rcf2p, Shy1p, and

Sco1p). None of the downregulated genes encoded core subunits. Notably, Cox15p is required for the hydroxylation of heme O to heme A, which is an essential prosthetic group for COX. This protein is highly conserved in bacteria, fungi, and humans, and mutations in the Cox15p coding sequence have been shown to result in deficiencies in respiratory growth (Barrientos et al. 2002). Meanwhile, *COA1* and *COA2* encode Coap1 and Coa2p, respectively, which are required for the assembly of COX and have been shown to interact with the assembly factor Shy1p, a mitochondrial inner membrane protein similar to human *SURF1* (involved in Leigh syndrome). Null mutations in these proteins lead to deficiencies in respiratory growth and the loss of COX activity (Pierrel et al. 2007, 2008). Finally, *RCF2* encodes a protein required for late-stage assembly of the Cox12p and Cox13p subunits (Strogolova et al. 2012), while *SCO1* encodes a copper-binding protein of the mitochondrial inner membrane required for COX activity and respiration (Nittis et al. 2001).

The final step of the OXPHOS pathway is catalyzed by F_0F_1-ATP synthase, located in the mitochondrial inner membrane. This enzyme, also known as complex V, is highly conserved among diverse organisms and utilizes proton motive force for ATP synthesis from ADP and inorganic phosphate. The complex consists of two major components, soluble F_1 and membrane-bound F_0, each of which is comprised of several subunits (Marsy et al. 2008; Kucharczky et al. 2009). In the present study, eight genes (*ATP2*, *ATP3*, *ATP5*, *ATP7*, *ATP11*, *ATP12*, *ATP16*, and *ATP18*) that encode subunits of F_0F_1-ATP synthase were significantly repressed in response to high inhibition level of BPA. Defects resulting in decreased abundance or impaired function of this multi-subunit enzyme can cause various neuromuscular disorders in humans, primarily in children (Kucharczky et al. 2009), and mutations in several subunits of F_0F_1-ATP synthase have been shown to affect COX biogenesis in yeast and human cells (Hadikusumo et al. 1988; Marsy et al. 2008).

In addition to the five enzyme complexes of OXPHOS, several genes associated with the electron carriers coenzyme Q and cytochrome C were also downregulated. Of these, *COQ1*, *COQ2*, *COQ4*, *COQ6*, *COQ9*, and *CAT5*, which encode proteins associated with coenzyme Q, were significantly repressed. Coenzyme Q, also known as the ubiquinone biosynthetic pathway, transfers electrons from complex I and/or II to complex III of the mitochondrial inner membrane (González-Mariscal et al. 2014).

Coq2 is a highly conserved protein that catalyzes the second step in ubiquinone, and mutations in its human ortholog were implicated in coenzyme Q10 deficiencies (Forsgren et al. 2004; Quinzii et al. 2006). *COQ6* encodes a putative flavin-dependent monooxygenase involved in ubiquinone biosynthesis, and the human homolog of this protein has been implicated in steroid-resistant nephrotic syndrome and can complement yeast null mutants (Heeringa et al. 2011). Meanwhile, cytochrome c transfers electrons from ubiquinol cytochrome-c reductase to COX during cellular respiration. Notably, reduced expression of the proteins that comprise cytochrome c, *CYC1*-cytochrome c isoform 1, and *CYC7*-cytochrome c isoform 2, the latter of which is associated with the electron carrier of the mitochondrial inner membrane, was also observed in response to the high inhibition concentration of BPA. Consistent with this observation, these genes were found to be repressed in yeast cells exposed to amphotericin B (Zhang et al. 2002). The human homolog (*CYC1*) of these paralogous genes has been implicated in insulin-responsive hyperglycemia (Gaignard et al. 2013).

3.2.2.2. Exposure to high inhibition concentrations of BPA results in downregulation of TCA cycle-related genes and mitochondrial components

Five genes associated with the TCA cycle were observed to be downregulated in *S. cerevisiae* cells exposed to the high inhibition concentration of BPA. Among these, *CIT1* encodes citrate synthase, which catalyzes the condensation of acetyl-CoA and oxaloacetate to citrate, the first reaction of the TCA cycle, while *KGD1* and *KGD2* encode components of the mitochondrial alpha-ketoglutarate dehydrogenase complex, which catalyzes the oxidative decarboxylation of alpha-ketoglutarate via succinyl-CoA to succinate. *MDH1* and *MDH2* encode mitochondrial malate dehydrogenase and cytoplasmic malate dehydrogenase, respectively (Kregiel 2012). Mdh1p also plays a role in the NADH shuttle pathway that regulates the NAD/NADH ratio in the cytoplasm and mitochondria. Overexpression of Mdh1p has been shown to extend the replicative lifespan, suggesting that this shuttle pathway plays a major role in calorie restriction-mediated lifespan extension (Easlon et al. 2008).

In contrast to our current findings, previous studies have shown that genes encoding proteins necessary for respiration and energy production are overexpressed under

different stress conditions. This is thought to reflect the demand for ATP for stress defense; however, genes encoding respiration components are not overexpressed under all stressful stimuli (Gasch 2002). In our study, various genes involved in OXPHOS and the TCA cycle were significantly repressed upon exposure to high inhibition level of BPA. Given that several of these genes are homologous/orthologous to loci encoded by higher eukaryotes, especially humans, these findings suggest that BPA may cause defects in mitochondrial processes that are analogous to mitochondrial dysfunctions implicated in the etiology of many complex human diseases (Kucharczky et al. 2009; Diaz 2010; Iwata et al. 2012; Gaignard et al. 2013; Kluckova et al. 2013). Moreover, the possible BPA-mediated repression of respiratory processes may contribute for the inhibitory effects on growth compared to unexposed yeast cells.

Several genes associated with the mitochondrial large subunit (*MRPL1*, *MRPL3*, *MRPL13*, *MRPL15*, *MRPL17*, *MRPL24*, *MRPL32*, and *MRPL35*), mitochondrial small subunit (*MRPS5*, *MRPS35*, *RSM24*, and *RSM25*), mitochondrial elongation (*MEF1* and *MEF2*), protein sorting and insertion (*SAM37*, *SAM50*, *MBA1*, and *MSA1*), and other important mitochondrial processes were also repressed in *S. cerevisiae* treated with 300 mg/L BPA.

3.2.2.3. BPA inhibits the expression of autophagy-related genes

Five genes (*ATG3*, *ATG4*, *ATG17*, *ATG19*, and *ATG33*) encoding proteins involved in autophagy were significantly downregulated in response to the high inhibition concentration of BPA. Autophagy is a highly conserved and stress-induced eukaryotic pathway in which cytoplasmic contents are transported in bulk to lysosomes for degradation into amino acids and fatty acids that can then be utilized for the synthesis of new proteins or can be oxidized by mitochondria to produce energy for cell survival during starvation (Chen and Klionsky 2011). Approximately 30 autophagy-related (Atg) proteins have been identified in *S. cerevisiae* to date, and null mutations in most of these proteins result in cell death under nutrient starvation conditions by inhibiting autophagy (Suzuki and Ohsumi 2007). Gomes and Scorrano (2011) showed that mitochondrial elongation during starvation protects mitochondria from autophagic degradation, and that normal mitochondria are degraded faster than elongated mitochondria in response to autophagic stimuli. As previously stated, two mitochondrial elongation factors were

repressed along with autophagic proteins in *S. cerevisiae* treated with 300 mg/L BPA.

3.2.2.4. Exposure to 300 mg/L BPA results in downregulation of nucleobase-containing metabolic processes

As observed in *S. cerevisiae* cells treated with low inhibition level of BPA, various nucleobase-containing small molecule metabolic processes were affected by the high inhibition concentration of BPA. Specifically, four genes (*BNA1*, *BNA2*, *BNA4*, and *BNA6*) involved in *de novo* biosynthesis of nicotinamide adenine dinucleotide (NAD) were significantly repressed under this condition. NAD is an essential cofactor for energy metabolism and is an important substrate in many biological processes, including DNA repair, transcriptional regulation, signaling pathways, age-associated diseases, and life span extension (Lin and Guarente 2003). Along with the downregulation of several genes related to OXPHOS and TCA-cycle, repression of these genes suggests that energy metabolism may be affected. Additionally, four genes (*ADE2*, *ADE12*, *ADE13*, and *ADE17*) associated with *de novo* purin biosynthesis were also significantly repressed under the high inhibition condition.

3.2.2.5. Exposure to 300 mg/L results in downregulation of genes associated with N-linked glycosylation and ergosterol biosynthesis

Several genes encoding mannosyltransferases associated with the *N*-linked glycosylation pathway and proteins involved in glycogen metabolism were downregulated upon exposure to 300 mg/L. *ALG2* encodes a mannosyltransferases that catalyzes the addition of the second and third mannose moieties to the growing oligosaccharide chain during lipid-linked oligosaccharide biosynthesis (O'Reilly et al. 2006), while *ALG9* encodes a mannosyltransferase that catalyzes the addition of the seventh and ninth mannose moieties to the growing oligosaccharide during *N*-linked glycosylation (Frank et al. 2004). The human homolog of *ALG9* (also referred to as *ALG9*) is capable of complementing yeast null mutants, and mutations in this homolog cause type 1 congenital disorders of glycosylation in humans (Frank et al. 2004). *OCH1* encodes a mannosyltransferase that adds a mannose moiety to core *N*-linked oligosaccharides upon their arrival in the Golgi apparatus. Notably, deletion or depletion of this gene results lethality or slow cell growth in *S. cerevisiae* (Lehle et al.

1995). Furthermore, we detected decreased expression of two genes (*MNN5* and *KTR1*) that encode alpha-1,2-mannosyltransferases, as well as four genes (*GSY1*, *GSY2*, *GLC3*, and *GPH1*) involved in glycogen metabolism in the 300 mg/L BPA culture. Glycogen is a branched polymer of glucose that functions as storage of carbon and energy in many taxa. *GSY1* and *GSY2* encode two glycogen synthases that are induced by glucose limitation, nitrogen starvation, stationary phase, and by environmental stresses such as osmotic stress and heat shock (Wilson et al. 2010). Meanwhile, *GLC3* and *GPH1* encode a glycogen branching enzyme that is involved in glycogen accumulation and a glycogen phosphorylase that is required for the mobilization of glycogen, respectively.

Four genes (*ERG13*, *ERG20*, *ERG26*, and *ERG28*) associated with ergosterol biosynthesis, which is the primary membrane sterol found in yeast cells and plays a structural role in the yeast cell membrane, similar to cholesterol in mammalian systems, were downregulated upon exposure to 300 mg/L BPA. In contrast, the gene encoding inositol-3-phosphate synthase (*INO1*), which contributes to phospholipid synthesis, was upregulated under this condition. Notably, the concurrent downregulation of ergosterol biosynthesis genes and upregulation of genes associated with phospholipid synthesis, including *INO1*, was previously found to be an indication of cell membrane reconstruction in response to membrane perturbation caused by exposure to amphotericin B (Zhang et al. 2002).

Meanwhile, the majority of the genes that were upregulated in response to 300 mg/L BPA were associated with RNA processing (rRNA processing, ribosomal large and small subunit biogenesis, and related processes), responses to chemicals, ion transport, transcription from the RNA polymerase II promoter, and mitosis and associated processes (Table 3.6).

Table 3.6 Selected biological processes significantly enriched among the genes upregulated in *S. cerevisiae* cells exposed to 300 mg/L bisphenol A (BPA)

GOID	GO term	Frequency	Gene(s)
6364	rRNA processing	67/606 genes 11.1%	*MAK16*, *UTP20*, *MAK5*, *SPB1*, *KRR1*, *SRD1*, *BUD23*, *NOP1*, *DBP10*, *SAS10*, *NHP2*, *RRP8*, *RRP1*, *BFR2*, *ESF1*, *UTP5*, *NUG1*, *LOC1*, *CGR1*, *SPT4*, *NOP7*, *ENP2*, *MTR3*, *NSR1*, *RPP1*, *SSF1*, *LRP1*, *GAR1*, *RIX1*, *FAF1*, *BMT5*, *HCA4*, *RPS14B*, *DHR2*, *UTP11*, *EBP2*, *RPF2*, *DRS1*, *SOF1*, *FYV7*, *MDN1*, *EMG1*, *PWP1*, *UTP13*, *BUD22*, *RNT1*, *HAS1*, *RLP7*, *IMP4*, *DBP2*, *JJJ1*, *KRI1*, *RCL1*, *REX4*, *UTP23*, *NOB1*, *RIO1*, *PNO1*, *RRS1*, *SNU66*, *RRP12*, *NOP4*, *NAN1*, *NOP53*, *NIP7*, *DIM1*, *MRD1*
42221	response to chemical	43/606 genes 7.1%	*NRG2*, *FRM2*, *TRX3*, *YCR102C*, *RPN4*, *HBT1*, *SNQ2*, *NRG1*, *PPH3*, *UPC2*, *ADR1*, *CTA1*, *SVF1*, *PDR15*, *MIG3*, *AGA2*, *MIG2*, *FRA2*, *SLI1*, *VMR1*, *YHK8*, *URM1*, *BAR1*, *YAP5*, *SIP4*, *YJL144W*, *LTV1*, *ATR1*, *FET3*, *SIP18*, *ASI3*, *MFA2*, *PDR16*, *HUB1*, *YNR064C*, *PDR5*, *TIM18*, *PDR10*, *PIP2*, *GPB1*, *USV1*, *YAR1*, *CE103*

Table 3.6 continued

42274	ribosomal small subunit biogenesis	39/606 genes 6.4%	*UTP20*, *KRR1*, *BUD23*, *SAS10*, *NOP6*, *BFR2*, *UTP5*, *LOC1*, *NOP7*, *ENP2*, *NSR1*, *FAF1*, *RPS14B*, *DHR2*, *RRP14*, *UTP11*, *LTV1*, *UTP30*, *SOF1*, *FYV7*, *EMG1*, *UTP13*, *BUD22*, *TMA23*, *HAS1*, *IMP4*, *KRE33*, *KRI1*, *RCL1*, *UTP23*, *NOB1*, *RIO1*, *PNO1*, *RRS1*, *RRP12*, *NAN1*, *YAR1*, *DIM1*, *MRD1*
6366	transcription from RNA polymerase II promoter	34/606 genes 5.6%	*TOD6*, *NRG2*, *RPN4*, *NRG1*, *UPC2*, *ADR1*, *CRF1*, *MET32*, *YAP6*, *NCB2*, *MIG3*, *AFT1*, *MIG2*, *FRA2*, *SPT4*, *SIP4*, *VHR1*, *MET28*, *YAP5*, *GON7*, *YKE2*, *DAT1*, *RNT1*, *MKS1*, *GIM3*, *NRD1*, *STD1*, *GAC1*, *YOR338W*, *PIP2*, *CUP9*, *USV1*, *RPO26*, *YHR177W*
42273	ribosomal large subunit biogenesis	33/606 genes 5.4%	*MAK16*, *MAK5*, *REI1*, *SPB1*, *DBP10*, *SYO1*, *RRP8*, *SSF2*, *LOC1*, *NSA1*, *NOP7*, *SDA1*, *SSF1*, *RIX1*, *YVH1*, *ALB1*, *RIX7*, *RPF2*, *DRS1*, *MDN1*, *RSA3*, *HAS1*, *JJJ1*, *REX4*, *YTM1*, *RRS1*, *NOP4*, *NOP53*, *NIP7*, *RRP14*, *RLP24*, *RLP7*, *NOP15*

Table 3.6 continued

6811	ion transport	30/606 genes 5%	*SUL1*, *PHO89*, *ADY2*, *ENA5*, *CCC2*, *ATO3*, *AFT1*, *MEP1*, *BTN2*, *MPC3*, *DUR3*, *CTR2*, *SFC1*, *FAT3*, *FRE2*, *TPO1*, *FRE6*, *FRE1*, *CTR3*, *ATR1*, *FET3*, *PDR16*, *FRE7*, *ENB1*, *RSB1*, *MCH5*, *PUT4*, *MFM1*, *HUT1*, *CTR1*
48285	organelle fission	29/606 genes 4.8%	*RAD61*, *PPH3*, *CIN8*, *MEI4*, *MAM1*, *DMC1*, *HOP2*, *RIM8*, *AFT1*, *MAD1*, *RCK1*, *MND1*, *SPO11*, *SAE3*, *NDT80*, *REC104*, *YVH1*, *MAD2*, *EBP2*, *REC102*, *REC114*, *PDR16*, *SPO21*, *NDJ1*, *RIO1*, *GAC1*, *GPN2*, *MEK1*, *SPO19*
71554	cell wall organization or biogenesis	21/606 genes 3.5%	*SPS22*, *FMP45*, *DIT2*, *DIT1*, *SPS2*, *SPS1*, *SPS100*, *PFS1*, *YVH1*, *GON7*, *PIR3*, *OSW2*, *CRR1*, *SPO77*, *RNT1*, *LDS2*, *SPO21*, *HPF1*, *SSP2*, *OSW1*, *MUM3*
278	mitotic cell cycle	19/606 genes 3.1%	*REI1*, *BUD23*, *RAD61*, *MET32*, *CDC40*, *CIN8*, *AFT1*, *MAD1*, *ZPR1*, *SDA1*, *MAD2*, *SAP185*, *SLD2*, *BUD20*, *JNM1*, *RIO1*, *GAC1*, *GPN2*, *CLB2*

Table 3.6 continued

9451	RNA modification	18/606 genes 3%	*KTI11*, *SPB1*, *BUD23*, *NOP1*, *NHP2*, *RRP8*, *TRM1*, *TAD1*, *GAR1*, *URM1*, *BMT5*, *TAD2*, *SAP185*, *EMG1*, *DUS1*, *TRM11*, *PPM2*, *DIM1*
51169	nuclear transport	18/606 genes 3%	*ECM1*, *REI1*, *BUD23*, *SYO1*, *BCP1*, *NUG1*, *MAD1*, *SDA1*, *NMD3*, *RIX1*, *LTV1*, *SRP40*, *RIX7*, *BUD20*, *JJJ1*, *RRS1*, *NOP53*, *YAR1*
70271	protein complex biogenesis	16/606 genes 2.6%	*USO1*, *RBS1*, *DAD1*, *NCB2*, *TCA17*, *CIN8*, *SLD2*, *MIM2*, *YKE2*, *CTF13*, *CIN4*, *GIM3*, *NOB1*, *PNO1*, *CIN2*, *HPA2*
6520	cellular amino acid metabolic process	15/606 genes 2.5%	*LYS20*, *MET32*, *IRC7*, *MET13*, *STR3*, *HIS6*, *MET28*, *ARG3*, *AAT1*, *PUT1*, *ADI1*, *MET2*, *ARG1*, *CPA1*, *CAR1*
6397	mRNA processing	14/606 genes 2.3%	*AAR2*, *ECM2*, *MUD1*, *CDC40*, *SPT4*, *RPP1*, *CWC24*, *RNT1*, *SWT21*, *NRD1*, *HUB1*, *SME1*, *DED1*, *SNU66*
6325	chromatin organization	14/606 genes 2.3%	*NOP1*, *SIR2*, *LYS20*, *NGG1*, *ADR1*, *SIR4*, *IES6*, *PUF4*, *SPT4*, *YAP5*, *SWC7*, *NAT4*, *RNT1*, *HPA2*
6873	cellular ion homeostasis	13/606 genes 2.1%	*SNQ2*, *RRG1*, *CTH1*, *CCC2*, *SIT1*, *ARN2*, *CTR2*, *FRE6*, *TIS11*, *FET3*, *IZH4*, *PDR5*, *FRE3*
6401	RNA catabolic process	12/606 genes 2%	*CTH1*, *SUP35*, *PUF4*, *MTR3*, *LRP1*, *AIR1*, *TIS11*, *NGL3*, *DBP2*, *NRD1*, *TRF5*, *DCP1*

3.2.2.6. Exposure to 300 mg/L BPA results in enhanced expression of genes involved in ribosomal activity

Ribosomal biogenesis involves a complex series of processes, including synthesis, processing, and modification of rRNA and ribosomal proteins, followed by assembly of the components. Each of these processes is highly regulated and coordinated via association with other fundamental cellular activities, including cell division and growth, to prevent energy loss and imbalance. The ribosomes of *S. cerevisiae* consist of two ribonucleoprotein subunits: the small subunit (SSU, 40S) consists of one ribosomal RNA (18S rRNA) and 33 ribosomal proteins (r-proteins), while the large subunit (LSU, 60S) is comprised of three rRNAs (5S, 5.8S, and 25S) and 46 r-proteins. The SSU functions as the decoding center, bringing the mRNA and aminoacylated transfer RNAs (tRNAs) together, while the LSU mediates the peptidyltransferase reactions that catalyze peptide bond formation (Woolford Jr and Baserga 2013). A large number of ribosomes are required for cell growth and/or increases in cell bulk, and defects in the regulation of ribosomal assembly can have serious deleterious effects. Indeed, complete loss-of-function mutations in most assembly factors and r-proteins are lethal in yeast and higher organisms, and defects in ribosomal biogenesis are associated with several diseases in humans, including cancer, anemia, and aging (Lempiainen and Shore 2009; Woolford Jr and Baserga 2013). In the current study, we observed enhanced expression of 67 genes associated with rRNA processing, 39 genes associated with ribosomal SSU biogenesis and related processes, and 33 genes associated with ribosomal LSU biogenesis and related processes in *S. cerevisiae* upon exposure to 300 mg/L BPA. Additionally, several genes involved in processes linked to ribosomal biogenesis, including RNA modification (18 genes), protein complex biogenesis (16 genes), mRNA processing (14 genes), and RNA catabolic processes (12 genes), were affected by exposure to the high inhibition concentration of BPA. These findings contrast with those of previous studies, which observed significant downregulation of ribosomal biogenesis and assembly genes in yeast in response to different stresses (Yu et al. 2010; Soontorngun 2016). Moreover, referring to previous results (Causton et al. 2001), it was inferred that repression of ribosomal genes is a general feature of the environmental stress response (ESR) (Yu et al. 2010). Most ESR genes exhibit similar responses to environmental stresses, and induction of ESR genes has been shown to result in

decreased growth rates, indicating that the stress response and changes in growth rate involve similar factors (Regenberg et al. 2006; Ho and Gasch 2015). Interestingly, consistent with these findings, exposure to BPA resulted in decreased growth rates in *S. cerevisiae*; however, this stress also resulted in upregulation of most ribosomal biogenesis and assembly genes, as well as rRNA processing genes. These observations may indicate that cells attempt to overcome BPA toxicity, particularly the decreased growth rate, by upregulating ribosomal biogenesis.

3.2.2.7. Exposure to a high inhibition concentration of BPA results in upregulation of chemical-response genes

In *S. cerevisiae* cells exposed to the high inhibition concentration of BPA, a substantial percentage (7.1%) of induced genes were involved in the response to chemicals, including genes encoding transporters of the ABC superfamily (*PDR5*, *PDR10*, *PDR15*, *PDR16*, *SNQ2*, and *VMR1*). In addition, we detected significantly enhanced expression of *TPO1* and *YHK8*, which encode H^+ antiporters of the major facilitator superfamily involved in MDR. These findings are therefore consistent with those of previous studies, in which cycloheximide and isooctane (Nishida et al. 2014), alachlor (Gil et al. 2011) and *p*-anisaldeyhde (Yu et al. 2010) toxicity resulted in induction of several ABC genes. We postulated that BPA may trigger the PDR network in yeast cells. Moreover, we speculated that certain genes induced in our study may aid in protecting yeast cells against BPA exposure by pumping BPA molecules out of the cytoplasm, similar to previously observed responses to alachlor and other xenobiotics (Sa-Correia et al. 2009; Gil et al. 2011).

3.2.2.8. Exposure to the high inhibition concentration of BPA promotes the expression of genes involved in iron and copper acquisition and sulfur utilization

Iron and copper are essential nutrients that act as cofactors in numerous biochemical reactions involving the transfer of electrons during respiration, iron acquisition, and protection against oxidative stress. However, these metals are both found as insoluble complexes in the environment and, owing to the generation of destructive hydroxyl free radicals, are toxic in the presence of oxygen. Accordingly, organisms have evolved

sophisticated systems to transport iron and copper into the cell and to maintain intracellular concentrations at non-toxic levels. While iron is reduced at the cell surface by membrane spanning ferric reductases, copper uptake requires high-affinity copper transporters, which are functionally redundant to ferric reductases. Ferric reductases and copper transporters are transcriptionally induced upon iron and copper depletion (Marvin et al. 2003). In our study, 11 genes associated with iron uptake (*FRE1*, *FRE2*, *FRE3*, *FRE6*, and *FRE7*), copper transport (*CTR1*, *CTR2*, and *CTR3*), and transcriptional regulation of ferric reductase and copper transporters (*AFT1*, *FET3*, and *CCC2*) were significantly induced upon exposure to 300 mg/L BPA. These data suggest that BPA directly prevents iron and copper uptake by cells or interferes with these ions indirectly, thereby reducing nutrient allocation to the appropriate compartments. These findings may also explain the observed repression of the OXPHOS process in the presence of BPA, as iron and copper are essential for electron transfer and as a cofactor for cytochrome oxidase, respectively (Rustici et al. 2007).

We also detected significant upregulation of several genes (*MET2*, *MET13*, *MET28*, and *MET32*) encoding DNA-binding transcription factors associated with the sulfur assimilation pathway (also known as the methionine biosynthetic pathway), which plays a central role in metabolism and growth control in yeast. Meanwhile, *STR3*, which encodes the peroxisomal cystathionine beta-lyase responsible for converting cystathionine into homocysteine in the transsulfuration pathway, was also induced upon exposure to the high inhibition concentration of BPA. Increased levels of methionine have been shown to influence various cellular functions such as cell division, survival under starvation, redox homeostasis, and oxidative stress responses (Petti et al. 2012). Based on these results and those of previous studies of herbicides (i.e., alachlor) (Gil et al. 2011), we postulated that BPA toxicity promotes adenosylmethionine biosynthesis because *S*-adenosylmethionine plays a protective role in yeast and mammalian cells under stress (Malakar et al. 2008; Cavallaro et al. 2010). These data suggest that BPA interacts with the sulfur assimilation pathway, which could comprise a toxicological side effect of BPA in mammalian disorders associated with sulfur metabolism, consistent with the findings of previous studies examining the effects of alachlor (Gil et al. 2011). Moreover, these transcription factors may be induced to overcome oxidative stress owing to BPA, as methionine abundance is associated with the oxidative stress

response.

3.2.2.9. Exposure to the high inhibition concentration of BPA results in upregulation of genes involved in replication

As observed for the low inhibition concentration group, several genes associated with spindle assembly and chromosomal segregation were upregulated in *S. cerevisiae* cells exposed to 300 mg/L BPA. We also detected significant induction of various genes associated with these processes, including *CIN2*, *CIN4*, and *CIN8* (also induced at the low inhibition concentration), which encode proteins involved in the spindle assembly checkpoint and chromosome segregation (Gheber et al. 1999; Hoyt et al. 1990), *MAD1* (also induced at the low inhibition concentration) and *MAD2*, which encode components of the spindle assembly checkpoint complex (Jin et al. 1998), and *IES6*, which encodes a component of the chromatin remodeling complex involved in the regulation of chromosome segregation and the maintenance of normal centromeric chromatin structure (Chambers et al. 2012). The consistency of the results obtained using high and low inhibition concentrations of BPA demonstrate that exposure to this compound affects spindle assembly and chromosome segregation, and triggers the expression of genes associated with these mechanisms. As such, yeast cells may naturally increase the abundance of these proteins to prevent BPA-related damage. Moreover, we detected significantly increased expression of several genes associated with chromatin modification, such as *HPA2*, *NAT4*, and *NGG1*, which encode histone acetyltransferases, and *SIR2* and *SIR4*, which encode histone deacetylases. Likewise, the *CLB2*, *CDC40*, *RIO1*, *MFA2*, and *YHR177W* genes, which encode proteins involved in cell cycle progression, were induced in response to the high inhibition concentration of BPA. We speculate that increased expression of these genes indicates that BPA exposure promotes cell cycle progression and DNA packaging.

3.2.3. Comparison of low and high inhibition concentrations of BPA

Several genes and processes/pathways were significantly affected by both concentrations of BPA. The most prominently repressed genes in the 50 mg/L BPA group were associated with mitochondrial membrane organization, ion transport, nucleobase-containing small molecule metabolic processes, and carbohydrate

metabolism, while exposure to 300 mg/L BPA resulted in repression of genes associated with mitochondrion organization and associated processes, such as the OXPHOS system, TCA cycle, mitochondrial small and large subunits, nucleobase-containing small molecule metabolic process, autophagy, and ergosterol biosynthesis. Among them nucleobase-containing small molecule metabolic processes was the most repressed biological process with 51 genes upon exposure to 300 mg/L BPA while carbohydrate transport was the least affected process with 3 genes and found in the 50 mg/L BPA group (Figure 3.5). Conversely, the genes induced upon exposure to 50 and 300 mg/L BPA were primarily associated with transcription from the RNA polymerase II promoter, mitosis and associated processes, responses to chemicals and DNA damage, and DNA repair, and with RNA processing (rRNA processing, ribosomal large and small subunit biogenesis and related processes), responses to chemicals, ion transport, transcription from the RNA polymerase II promoter, and mitotic cell cycle and associated processes, respectively. Within these processes, DNA repair was the least induced process with 7 genes upon exposure to low inhibition concentration of BPA, and rRNA processing was the most induced biological process with 67 genes and found in the high inhibition concentration group (Figure 3.5).

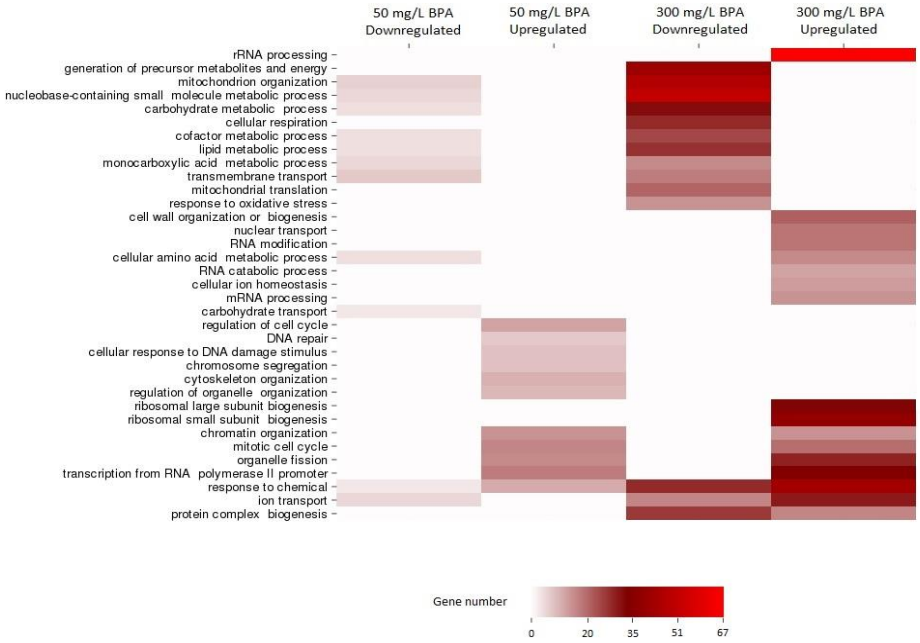
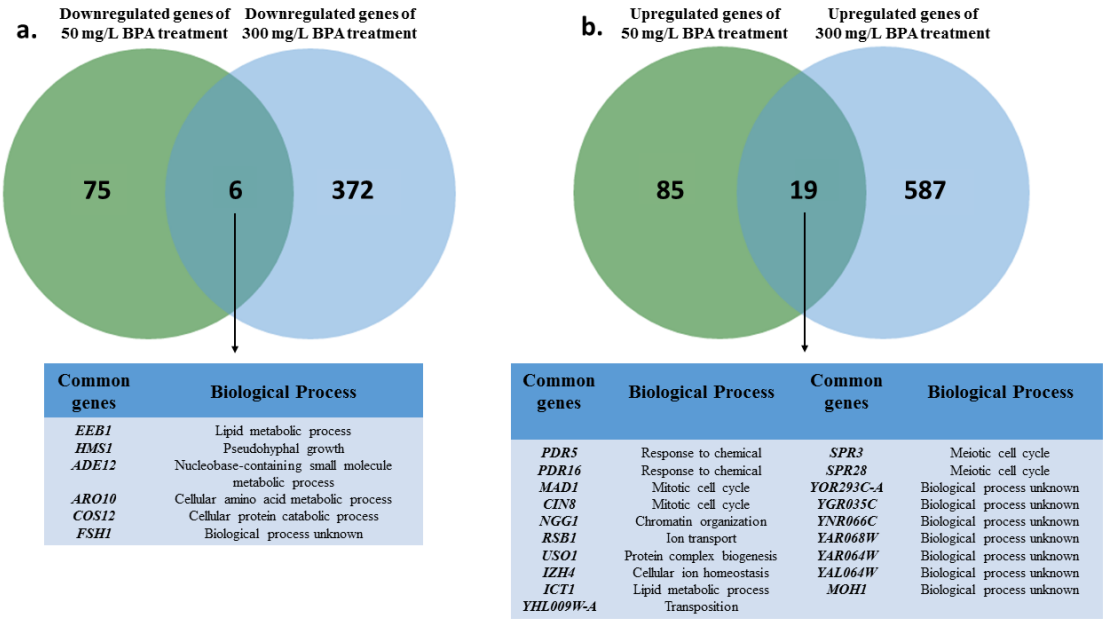


Figure 3.5 Comparison of the significantly enriched biological processes between 50 and 300 mg/L BPA exposure

Although certain processes were affected by both concentrations, including mitochondria, nucleobase-containing small molecule metabolic processes, transcription from the RNA polymerase II promoter, and mitosis and associated processes, the number and magnitude of the effected genes were distinct for each concentration. After 300 mg/L BPA exposure, there were severe effects on various processes and several genes, with substantial changes in expression. Meanwhile, 50 mg/L BPA exposure resulted in more modest changes in expression of small number of genes. Besides, considering downregulated genes, there were only six common genes between the low and high inhibition concentrations, while there were 19 common genes between upregulated genes of 50 mg/L and 300 mg/L BPA treatments (Figure 3.6). These results demonstrate that yeast cells respond to BPA in a concentration-dependent manner via different genes. Several studies have indicated that the demand for BPA has been increasing gradually (Careghini et al. 2015; Im et al. 2015; Gerona et al. 2016), and although BPA may be biodegradable in the ecosystems (Careghini et al. 2015), it can accumulate in natural environments due to its continuous release which makes it a potential threat to ecosystems (Careghini et al. 2015; Zhou et al. 2016).



Common genes	Biological Process
EEB1	Lipid metabolic process
HMS1	Pseudohyphal growth
ADE12	Nucleobase-containing small molecule metabolic process
ARO10	Cellular amino acid metabolic process
COS12	Cellular protein catabolic process
FSH1	Biological process unknown

Common genes	Biological Process	Common genes	Biological Process
PDR5	Response to chemical	*SPR3*	Meiotic cell cycle
PDR16	Response to chemical	*SPR28*	Meiotic cell cycle
MAD1	Mitotic cell cycle	*YOR293C-A*	Biological process unknown
CIN8	Mitotic cell cycle	*YGR035C*	Biological process unknown
NGG1	Chromatin organization	*YNR066C*	Biological process unknown
RSB1	Ion transport	*YAR068W*	Biological process unknown
USO1	Protein complex biogenesis	*YAR064W*	Biological process unknown
IZH4	Cellular ion homeostasis	*YAL064W*	Biological process unknown
ICT1	Lipid metabolic process	*MOH1*	Biological process unknown
YHL009W-A	Transposition		

Figure 3.6 Common downregulated and upregulated genes upon exposure to 50 mg/L and 300 mg/L BPA

3.2.4. Validation of microarray data of BPA by quantitative real-time RT-PCR analysis

To validate the results of our transcriptomic analyses, we subjected the RNA samples used in the microarray experiments to quantitative real-time RT-PCR analysis. We selected 11 *S. cerevisiae* genes that exhibited either decreased or increased expression upon exposure to the high inhibition concentration of BPA (>70% inhibition in cell number). The following criteria were used for selection of these genes: 1) included in a statistically significantly overrepresented biological process and/or 2) exhibited high levels of differential expression (applying a 1.5-fold cutoff) based on the microarray data. Of these 11 genes, five were repressed (*NDI1*, *SDH1*, *QCR2*, *COX4*, and *ATP3*, which are involved in the OXPHOS system) and six were induced [*PDR5* and *SNQ2*, ABC superfamily; *UTP23* and *NOP15*, ribosomal small and large subunit biogenesis, respectively; *CIN2*, GTPase-activating protein (GAP) for Cin4p; and *PHO89*, plasma membrane Na+/Pi cotransporter] upon exposure to 300 mg/L BPA. Notably, only *PHO89* did not meet the first criterion. This gene was selected owing to its markedly increased expression in response BPA exposure. Meanwhile, *CCW12* was used as a housekeeping gene. *CCW12* encodes a mannoprotein required for cell wall integrity during budding and the formation of mating projections (Ragni et al. 2011); according to our microarray data, there were no changes in the mRNA expression of this gene in response to BPA exposure. Overall, the microarray data and quantitative real-time RT-PCR data were highly consistent (with a Pearson correlation of 0.927) for the 11 genes tested (Table 3.7). These findings therefore verify that our microarray results provide an accurate reflection of changes in gene expression in *S. cerevisiae* in response to BPA exposure.

Table 3.7 Comparison of gene expression levels of BPA using quantitative real-time RT-PCR and microarray data

Gene	Description of gene product	Real-time RT-PCR		Microarray	
		Fold change	P value	Fold change	P value
NDI1	Ubiquinone oxidoreductase	-2.8	2.35E-04	-2.2	5.08E-05
SDH1	Succinate dehydrogenase	-3.5	2.44E-06	-2.7	4.68E-07
QCR2	Cytochrome c oxidoreductase	-2.2	1.22E-06	-2.1	3.14E-05
COX4	Cytochrome c oxidase	-2.7	1.60E-05	-1.8	7.90E-05
ATP3	ATP synthase	-2.1	7.29E-06	-1.9	1.64E-05
PDR5	Plasma membrane ATP-binding cassette (ABC) transporter	+2.5	3.15E-04	+1.6	3.70E-04
SNQ2	Plasma membrane ATP-binding cassette (ABC) transporter	+3.3	8.67E-08	+1.9	8.44E-05
UTP23	U three-associated protein	+1.9	3.41E-06	+1.8	2.35E-04
NOP15	NucleOlar protein	+1.9	1.91E-06	+2.0	2.80E-05
CIN2	GTPase-activating protein	+14.8	4.77E-09	+3.9	7.14E-06
PHO89	Plasma membrane Na+/Pi cotransporter	+16.6	9.47E-11	+10.4	3.56E-06

3.3. The effects of NP on the gene expression profiles of *S. cerevisiae*

The transcription profiles of yeast cells were assessed upon exposure to two different concentrations of NP. 1 mg/L NP was used as low inhibition concentration, while 5 mg/L NP referred to high inhibition concentrations. For gene expression analyses, yeast cells were exposed to these concentrations for two time intervals. In addition to 180 min treatment which was also used for BPA treatment, we here analyzed an additional timepoint which is 120 min, because previous studies showed that drug-specific changes in yeast gene expression typically appear a few hours after exposure (Gil et al. 2011; Gasch and Werner-Washburne 2002).

3.3.1. Analysis of the toxic effects of exposure to 1 mg/L NP

DNA microarray analysis revealed that a total of 187 genes were differentially expressed in yeast exposed to the 1 mg/L NP for 120 min compared with the control. Of these genes, 63 were downregulated and 124 were upregulated. On the other hand, a total of 103 genes were differentially expressed in yeast exposed to 1 mg/L NP for 180 min compared with the control and of these genes, 56 were repressed while 47 were induced (Figure 3.7). A complete list of these genes and their expression levels can be found in Table S4 and Table S5.

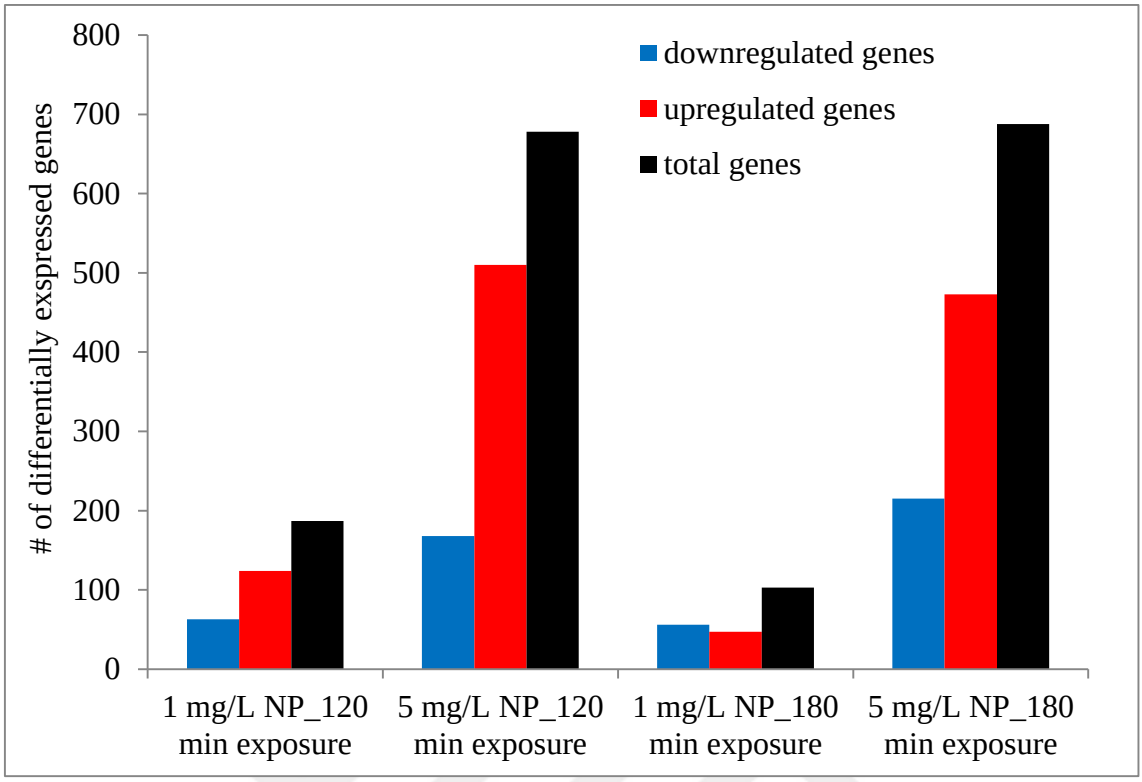


Figure 3.7 Number of differentially expressed genes under nonylphenol (NP) exposure

Many of the downregulated genes were associated with transport processes (particularly, transmembrane and ion), metabolic processes such as cellular amino acid and monocarboxylic acid metabolic processes in both exposure times. Besides, transcription from RNA polymerase was downregulated at 120 min exposure while carbohydrate metabolic process was repressed at 180 min exposure (Table 3.8).

Table 3.8 Selected biological processes significantly enriched among the genes downregulated in S. cerevisiae cells exposed to 1 mg/L nonylphenol (NP) for 120 and 180 minutes

120 minutes exposure			
GOID	**GO term**	**Frequency**	**Gene(s)**
6520	cellular amino acid metabolic process	11/63 genes 17.5%	*ARO10*, *LEU1*, *ARO9*, *BAT1*, *ILV3*, *BAT2*, *MAE1*, *ALT1*, *ILV5*, *LEU4*, *GLN1*

Table 3.8 continued

6811	ion transport	10/63 genes 15.9%	*BAP2*, *GIT1*, *PMP2*, *ZRT1*, *TPO2*, *OAC1*, *DIC1*, *SAM3*, *OPT2*, *ARR3*
55085	transmembrane transport	7/63 genes 11.1%	*FUI1*, *BAP2*, *GIT1*, *HXT15*, *HXT13*, *ZRT1*, MDH2
6366	transcription from RNA polymerase II promoter	6/63 genes 9.5%	*NRG1*, *MIG3*, *MIG1*, *RPI1*, *ZAP1*, *CUP9*
32787	monocarboxylic acid metabolic process	4/63 genes 6.3%	*ALD5*, *MAE1*, *MCT1*, *EEB1*
180 minutes exposure			
6811	ion transport	11/56 genes 19.6%	*GIT1*, *ZRT1*, *TPO2*, *AVT7*, *QDR2*, *ZRT2*, *DIC1*, *AQR1*, *TPO4*, *SAM3*, *OPT2*
55085	transmembrane transport	8/56 genes 14.3%	*FUI1*, *GIT1*, *HXT13*, *ZRT1*, *QDR2*, *ZRT2*, *AQR1*, *MDH2*
6520	cellular amino acid metabolic process	5/56 genes 8.9%	*ARO10*, *ARG5,6*, *ARO9*, *BAT2*, *ALT1*
32787	monocarboxylic acid metabolic process	4/56 genes 7.1%	*ALD5*, *POT1*, *EEB1*, *PDH1*
5975	carbohydrate transport	3/56 genes 5.4%	*HXT13*, *HXT1*, *HXT11*

3.3.1.1. Exposure to 1 mg/L NP results in downregulation of genes encoding sugar transporters

Three hexose transporter genes (*HXT1*, *HXT13*, and *HXT15*) were downregulated in response to 1 mg/L NP for 120 min. Of these, *HXT1* encodes a low-affinity glucose transporter which is induced in the presence of glucose and repressed when glucose is

limiting and it also plays role in the major facilitator superfamily (MFS) which will be discussed later, while *HXT13* and *HXT15* encodes high-affinity glucose transporters which are induced by low levels of glucose and repressed by high levels of glucose (Özcan and Johnston 1999). *HXT1* and HXT13 were also repressed in response to low levels of NP for 180 min exposure along with *HXT11*. This finding suggests that there may still be sufficient glucose for the growth of yeast cells exposed to NP, as it was speculated in the obtained data from BPA treatment. Also, we speculated that although there may be still glucose in the environment, yeast cells may balance uptake of glucose by regulating both low- and high-affinity hexose transporter genes at the same time.

3.3.1.2. NP may negatively affect amino acid biosynthesis

Two aromatic amino acid requiring genes (*ARO9* and *ARO10*) appeared to be significantly affected by NP exposure for both 120 and 180 min. These genes encode enzymes involved in catabolism of aromatic amino acids, tryptophan, phenylalanine, or tyrosine that are used as the main source for cellular nitrogen by *S. cerevisiae*. It was observed that in the presence of these aromatic amino acids *ARO9* was induced, while it was repressed in the absence of the amino acids (Iraqui et al. 1999).

Several genes related to branched-chain amino acid biosynthesis were found to be repressed after 120 min exposure while these genes were not affected at 180 min exposure time. Branched-chain amino acids are important nutrients which are metabolized by both eukaryotic and prokaryotic microorganisms as various sources such as carbon, nitrogen and energy. It was indicated that any metabolic disorder may lead acidosis (Shimizu et al. 2010). Two genes encoding the mitochondrial and cytosolic branched-chain amino acid aminotransferases and requiring for branched-chain amino acid biosynthesis and Ehrlich pathway amino acid catabolism, *BAT1* and *BAT2* (Kispal et al. 1996) and one gene encoding a branched-chain amino acid permease involved in uptake of leucine, isoleucine and valine, *BAP2,* were significantly downregulated (Grauslund et al. 1995). It was observed that deletion of *BAT1* and/or *BAT2* causes branched-chain amino acid auxotrophy and severe growth retardation (Kispal et al. 1996). *ILV3* and *ILV5* which are also involved in branched-chain amino acid biosynthesis (Shimizu et al. 2010), were significantly downregulated. *LEU4* and *LEU1*, two genes responsible for the first and second steps in the leucine biosynthesis

pathway respectively (Baichwal et al. 1983), were also significantly repressed upon exposure to low inhibition concentration of NP for 120 min. This finding indicates that yeast cells may adapt to low levels of NP in time, because the expression level of these affected genes returned to pre-stimulated levels after 180 min exposure.

3.3.1.3. Exposure to NP results in downregulation of genes associated with zinc regulation

Zinc-regulated transporter genes were found to be affected by both time intervals. *ZRT1* and *ZAP1* were significantly downregulated at 120 min exposure time while *ZRT1* and *ZRT2* were repressed at 180 min exposure time. Zinc is an essential nutrient for all organisms because it is a crucial cofactor for several transcription factors, proteins including the ubiquitous zinc finger proteins, and many enzymes involved in six major functional enzyme classes (Zhao and Eide 1996; Gaither and Eide 2001). Organisms must keep the intracellular concentration of zinc at a certain amount, because lack of this nutrient may cause cells to growth slow (Gaither and Eide 2001; Eide 1997)

3.3.1.4. NP inhibits the expression of genes involved in phosphate metabolism

Inorganic phosphate is an essential nutrient for the synthesis of many cellular components including nucleic acids and phospholipids that are used in several biological processes, such as biomolecule synthesis, energy metabolism and protein modification (Wykoff and O'Shea 2001; Secco et al. 2012). Cells determine to undergo processes specifically growth according to the availability of nutrients in the environment, and inorganic phosphate is a growth limiting substrate for organisms (Secco et al. 2012). When the amount of phosphate is depleted, cells induce several genes encoding phosphate transporters which increase the uptake of phosphate in response to phosphate starvation and free inorganic phosphate is transported into the cytoplasm. These genes are regulated by PHO operon (Wykoff and O'Shea 2001; Kennedy et al. 2005; Secco et al. 2012). However, in *S. cerevisiae*, cell division and growth can be arrested in case of prolonged phosphate deficiency (Secco et al. 2012). In the present study, three genes involved in phosphate metabolism, *PHO5*, *PHO8*, and *PHO11*, were significantly downregulated upon exposure to low inhibition concentration of NP for 120 min. Two of these genes, *PHO5* and *PHO8* were also

downregulated at 180 min exposure to low levels of NP.

3.3.1.5. Exposure to 1 mg/L NP results in reduced expression of genes involved in the major facilitator superfamily (MSF)

MFS transporters are involved in MDR and can be classified into two groups according to transport classification system. The 12-spanner drug:H(+) antiporter DHA1 family is one these two groups. In yeast, the characterized MFS-MDR transporters actively transport a wide range of drugs and xenobotics from the cytosol to the out of the cell to protect the cell from their possible toxic effects (Sa-Correia et al. 2009; Dia et al. 2010). We found that four genes (*TPO2*, *TPO4*, *QDR2*, and *AQR1*) which are member of the 12-spanner drug:H(+) antiporter DHA1 family were downregulated in response to 1 mg/L NP after 180 min exposure. This result conflicts with that of previous observation obtained from alachlor toxicity resulted in enhanced expression of several MSF genes (Gil et al., 2011). Moreover, these genes have been showed to have a resistance to several cytotoxic compounds in *S. cerevisiae* (Dia et al. 2010). We speculated that low inhibition concentration of NP may inhibit MFS transporters activity within the cells rather than inducing the mechanism. Besides, yeast cells may regulate their respond by overexpression of drug resistance genes which is discussed in subsequent sections while MSF genes are repressed.

Meanwhile, the majority of the genes that were upregulated in response to exposure to 1 mg/L NP were associated with carbohydrate metabolic process, generation of precursor metabolites and energy, response to chemical, and ion transport in both exposure times. In addition, monocarboxylic acid and lipid metabolic processes were significantly upregulated after 120 min exposure time while organelle fission and cellular ion homeostasis were induced after 180 min exposure to low levels of NP (Table 3.9). Each of these functions are discussed in more depth in following sections.

Table 3.9 Selected biological processes significantly enriched among the genes upregulated in *S. cerevisiae* cells exposed to 1 mg/L nonylphenol (NP) for 120 and 180 minutes

120 minutes exposure			
GOID	**GO term**	**Frequency**	**Gene(s)**
5975	carbohydrate metabolic process	18/124 genes 14.5%	*MAL33*, *MAL32*, *GLC3*, *GIP2*, *GSY1*, *IGD1*, *HXK1*, *SUC2*, *TDH1*, *YJR096W*, *XYL2*, *PGM2*, *GID8*, *NDE1*, *CAT8*, *MLS1*, *GAC1*, *GPH1*
32787	monocarboxylic acid metabolic process	14/124 genes 11.3%	*HXK1*, *OLE1*, *TDH1*, *ELO1*, *FAS1*, *CAT2*, *NDE1*, *CAT8*, *MLS1*, *GOR1*, *ACC1*, *GLO4*, *CRC1*, *FAS2*
6091	generation of precursor metabolites and energy	12/124 genes 9.7%	*GLC3*, *GIP2*, *GSY1*, *IGD1*, *HXK1*, *LSC2*, *TDH1*, *PGM2*, *NDE1*, *GAC1*, *NCA2*, *GPH1*
42221	response to chemical	11/124 genes 8.9%	*PDR3*, *UPC2*, *HSP12*, *YGL039W*, *VMR1*, *YJR096W*, *GPX1*, *CSI1*, *GAD1*, *CAT8*, *PDR5*
6629	lipid metabolic process	10/124 genes 8.1%	*UPC2*, *OLE1*, *ELO1*, *FAS1*, ICT1, *PLB2*, *ACC1*, *GRE2*, *CRC1*, *FAS2*
6811	ion transport	9/124 genes 7.3%	*GEX1*, *MPC3*, *JEN1*, *FRE2*, *CTR3*, *PRM6*, *ENB1*, *RSB1*, *PUT4*
6811	ion transport	7/47genes 14.9%	*FRE1*, *CTR3*, *PRM6*, *FET3*, *FRE7*, *RSB1*, *CTR1*

Table 3.9 continued

180 minutes exposure			
42221	response to chemical	6/47 genes 12.8%	*NRG2*, *XBP1*, *LTV1*, *FET3*, *AGA1*, *PDR5*
6091	generation of precursor metabolites and energy	4/47 genes 8.5%	*MBR1*, *PET10*, *PGM2*, *GAC1*
48285	organelle fission	4/47 genes 8.5%	*IME4*, *SPO21*, *GAC1*, *IRC15*
6873	cellular ion homeostasis	4/47 genes 8.5%	*SIT1*, *FET3*, *PGM2*, *PDR5*
5975	carbohydrate metabolic process	3/47 genes 6.4%	*MAL32*, *PGM2*, *GAC1*

3.3.1.6. Exposure to the low inhibition concentration of NP promotes the expression of genes involved in iron and copper acquisition

In both exposure times to low inhibition concentration of NP, several genes associated with iron and copper acquisition were significantly induced. *FRE2* (iron uptake), *ENB1* (ferric enterobactin transporting), and *LSO1* (iron uptake) were affected after 120 min exposure while two genes involved in iron uptake (*FRE1* and *FRE7*), two genes involved in iron transport (*FIT1* and *SIT1*), one gene associated with transcriptional regulation of ferric reductase (*FET3*) were significantly upregulated upon exposure to 1 mg/L NP for 180 min. Moreover, *CTR1* and CTR3, genes associated with copper transport, were significantly induced after 180 min exposure to low inhibition concentration of NP, while only CTR3 was upregulated upon 120 min exposure time.

3.3.1.7. Exposure to 1 mg/L NP results in upregulation of genes involved in fatty acid biosynthesis

Fatty acids are key components that are used in several processes, such as synthesis of biological membranes, energy storage, and protein modification. Fatty acid biosynthesis

is conserved among organisms (Tehlivets et al. 2007). Two genes (*FAS1* and *FAS2*) encoding fatty acid synthetases that catalyze the synthesis of long-chain saturated fatty acids were significantly upregulated upon exposure to 1 mg/L NP for 120 min. Considering the role of fatty acids in membrane biosynthesis and upregulation of related genes, we speculated that NP may affect yeast cell membrane. It was also speculated that the induction of genes involved in fatty acid metabolism in response to amphotericin B might be a reflection to cell membrane disruption caused by the chemical (Agarwal et al., 2003).

3.3.1.8. NP induces the expression of autophagy-related genes

Contradictory to our observation from BPA exposure, four genes (*ATG7*, *ATG34*, *ATG39*, and *ATG40*) encoding proteins involved in autophagy were significantly upregulated in response to the low inhibition concentration of NP after 120 min exposure. As we previously indicated that autophagy is a stress-induced eukaryotic pathway in which cytoplasmic substances are transferred to lysosomes to be degraded into amino acids and fatty acids to be used for new protein biosynthesis or energy production for cell survival during starvation (Chen and Klionsky 2011). Moreover, null mutations in yeast autophagy-related (Atg) proteins have been showed to cause cell death under nutrient starvation conditions by inhibiting autophagy (Suzuki and Ohsumi 2007). This data showed that NP exposure may result in induction of Atg genes to balance lack of essential amino acids for cell survival, because as we previously indicated that the expression of several genes associated with various amino acid biosynthesis were significantly repressed. Besides, upregulation of some genes related to fatty acid biosynthesis may support this observation.

3.3.1.9. Exposure to 1 mg/L NP results in increased expression of genes involved in glycogen metabolic process

Glycogen metabolic process was significantly affected upon exposure to 1 mg/L NP for 120 min. Six genes (*GLC3*, *IGD1*, *GIP2*, *GAC1*, *GSY1*, and *GPH1*) related to synthesis, accumulation, and phosphorylation of glycogen were significantly upregulated. In *S. cerevisiae* and most of the organisms, glycogen is the main storage form of glucose. Glycogen metabolism is regulated according to growth phase of the cell. In the actively

growing cultures, glycogen is not found, however it accumulates in cells having starvation, passing in diauxic growth phase, or reaching to stationary phase. Besides, this polysaccharide begins to accumulate when the level of glucose in the environment goes below 50% (Rowen et al. 1992). We speculated that glucose may be depleted fast and starvation starts in cells exposed to NP compared to control cells and subsequently these genes may be induced. We also suggested that NP may induce glycogen metabolism to increase ATP consumption which can prevent a possible cell death caused by a hypothesized mechanism called "turbo design patway" (Blomberg, 2000**).** In this assumption, salt stress decreases cell growth rates and lower ATP demand which causes inorganic phosphate depletion that finally may lead to cell death.

3.3.1.10. NP promotes the expression of drug resistance genes

Four pleiotropic drug resistance genes (*PDR3, PDR5, YOR1*, and *VMR1*) were also significantly upregulated upon exposure to low inhibition concentration of NP for 120 min. This finding is consistent with those of our study that we observed from data obtained in BPA treatment and of previous studies, in which cycloheximide and isooctane (Nishida et al. 2014), alachlor (Gil et al. 2011) and p-anisaldeyhde (Yu et al. 2010) toxicity resulted in induction of several pleiotropic drug resistance genes.

3.3.1.11. Exposure to 1 mg/L NP results in upregulation of maltose related genes

Moreover, three maltose related genes (*MAL31*, *MAL32* and *MAL33*) were affected after 120 min exposure. MAL31 encodes maltose permease which is a high-affinity maltose transporter encoded in the MAL3 complex locus and member of the 12 transmembrane domain superfamily of sugar transporters. MAL32 encodes maltase that is inducible protein involved in maltose catabolism encoded in the MAL3 complex locus. MAL33 encodes MAL-activator protein which is a part of complex locus MAL3 (Chow et al. 1989).

3.3.1.12. Exposure to 1 mg/L NP results in enhanced expression of genes involved in arginine catabolism

Two genes associated with catabolism of arginine (*CAR1* and *CAR2*) were upregulated only in response to low inhibition concentration after 180 min exposure. Yeast cells can

use arginine as its sole nitrogen source in case of depletion the main nitrogen sources. Cells start to catabolize arginine in the cytosol by converting of arginine into urea and ornithine using Car1p arginase encoded by *CAR1*. Then, Car2p ornithine amino transferase which is encoded by *CAR2* transfers ornithine into L-glutamate gamma-semialdehyde (Messenguy and Dubois, 2000). We speculated that NP may partially affect the main nitrogen consumption and yeast cells catabolize arginine to overcome this.

3.3.2. Analysis of the toxic effects of exposure to 5 mg/L NP

Based on the DNA microarray analysis, 678 genes were differentially expressed in *S. cerevisiae* cells exposed to 5 mg/L NP compared to the control cells for 120 min. Of these genes, 168 were downregulated and 510 were upregulated (Figure 3.7). On the other hand, a total of 688 genes were differentially expressed in yeast upon exposure to 5 mg/L NP for 180 min. Of these genes, 215 were downregulated, while 473 were upregulated. A complete list of the differentially expressed genes in response to 5 mg/L NP exposure and their expression levels can be found in Table S6 and Table S7.

As shown in Table 3.10, a significant proportion of the downregulated genes at both exposure times were involved in transmembrane transport, cellular amino acid metabolic process, and ion transport. Moreover, several downregulated genes after 120 min exposure time were clustered in rRNA processing, mitotic cell cycle, and ribosomal small subunit, while most of the significantly repressed genes upon exposure to 5 mg/L NP for 180 min were associated with mitochondrion organization, nucleobase-containing small molecule metabolic process, and protein complex biogenesis.

Table 3.10 Selected biological processes significantly enriched among the genes downregulated in *S. cerevisiae* cells exposed to 5 mg/L nonylphenol (NP) for 120 and 180 minutes

120 minutes exposure			
GOID	**GO term**	**Frequency**	**Gene(s)**
6364	rRNA processing	16/168 genes 9.5%	*BFR2*, *UTP4*, *UTP22*, *NSR1*, *SSZ1*, *DBP8*, *BMT5*, *MPP10*, *URB1*, *DIP2*, *RRP5*, *HAS1*, *DBP2*, *IPI3*, *PUS7*, *MOT1*
55085	transmembrane transport	14/168 genes 8.3%	*FUI1*, *FUR4*, *YMC2*, *ERS1*, *HXT7*, *FCY21*, *QDR2*, *KCH1*, *SAM50*, *MDH2*, *NRT1*, *TIM50*, *PEX25*, *FEX2*
6520	cellular amino acid metabolic process	14/168 genes 8.3%	*MIS1*, *SHM1*, *HIS4*, *LYS4*, *ASP1*, *ARO10*, *HIS1*, *ILV1*, *LEU1*, *DED81*, *THR1*, *ARO9*, *PRO2*, *ARO7*
278	mitotic cell cycle	13/168 genes 7.7%	*BRN1*, *ARP10*, *HKR1*, *DOT1*, *BUD16*, *CLB1*, *CLB6*, *SPT6*, *SWE1*, *BFA1*, *PSE1*, *SGO1*, *RFC1*
6811	ion transport	13/168 genes 7.7%	*ERS1*, *HNM1*, *TPO2*, *QDR2*, *KCH1*, *OAC1*, *YBT1*, *HOL1*, *SMF1*, *TPO4*, *SAM3*, *FEX2*, *OPT2*
42274	ribosomal small subunit biogenesis	11/168 genes 6.5%	*BFR2*, *UTP4*, *UTP22*, *NSR1*, *DBP8*, *MPP10*, *DIP2*, *RRP5*, *HAS1*, *KRE33*, *NEW1*

Table 3.10 continued

180 minutes exposure			
7005	mitochondrion organization	19/215 genes 8.8%	*CBS1*, *GGC1*, *RRG1*, *QCR7*, *RML2*, *COX13*, *TIM21*, *MRPS35*, *PET54*, *RRM3*, *MEF2*, *OCT1*, *COX12*, *RPM2*, *IMP2*, *ATP25*, *YHM2*, *SAM50*, *MDM20*
55085	transmembrane transport	16/215 genes 7.4%	*FUI1*, *FUR4*, *ERS1*, *GGC1*, *BAP3*, *HXT7*, *ATP17*, *AFG1*, *FCY21*, *TIM21*, *QDR2*, *KCH1*, *SAM50*, *MDH2*, *NRT1*, *SUT2*
6811	ion transport	16/215 genes 7.4%	*FAT1*, *ERS1*, *BAP3*, *ATP17*, *TPO2*, *QDR2*, *KCH1*, *OAC1*, *YHM2*, *HOL1*, *SMF1*, *TPO4*, *FAA1*, *SAM3*, *TPO3*, *OPT2*
55086	nucleobase-containing small molecule metabolic process	16/215 genes 7.4%	*BNA4*, *ATP17*, *QCR7*, *COX4*, *QCR10*, *ERC1*, *COX6*, *QCR8*, *BNA1*, *CYC1*, *URA1*, *URA4*, *URA5*, *COX7*, *SER1*, *QCR2*
6520	cellular amino acid metabolic process	15/215 genes 7.0%	*BNA4*, *MIS1*, *SHM1*, *HIS4*, *IDP1*, *ASP1*, *ARO10*, *HIS1*, *SER2*, *ARO9*, *BNA1*, *MET22*, *SER1*, *ARO7*, *MRI1*
70271	protein complex biogenesis	13/215 genes 6.0%	*CBS1*, *QCR7*, *COX13*, *PET54*, *COX12*, *ATP25*, *SPC24*, *SAM50*, *SPC98*, *NUF2*, *HIR2*, *TRS33*, *YOP1*

3.3.2.1. Exposure to 5 mg/L NP results in reduced expression of genes member of the 12-spanner drug:H(+) antiporter DHA1 family

Four genes (*TPO2*, *TPO4*, *QDR2*, and *HOL1*) which are member of the 12-spanner drug:H(+) antiporter DHA1 family were significantly downregulated upon exposure to high level of NP for both exposure times. In addition to these genes, *TPO3* was affected at 180 exposure time point. This finding showed that both low and high inhibition concentrations affect MFS transporters that are involved in MDR.

3.3.2.2. Exposure to high inhibition concentration of NP inhibits the expression of genes associated with amino acid biosynthesis

As observed in response to 1 mg/L NP treatment, genes associated with aromatic amino acid requiring were significantly repressed upon exposure to high inhibition concentration of NP for both 120 and 180 min. 5 mg/L NP induced expression of *ARO7*, *ARO9*, and *ARO10*.

Moreover, some genes associated with histidine biosynthesis were also significantly downregulated upon exposure to 5 mg/L NP for 180 min. *HIS1* and *HIS4* are two genes related to histidine biosynthesis. *HIS1* encodes an ATP phosphoribosyltransferase that catalyzes the first step in histidine biosynthesis (Alifano et al. 1996), while *HIS4* encodes a multifunctional polypeptide that catalyzes the second, third, ninth and tenth steps (Keesey et al. 1979). It has been shown that mutations in *HIS1*, *HIS4* and other genes encoding enzymes involved in histidine biosynthesis lead histidine auxotrophy and sensitivity to copper, cobalt, and nickel salts (Pearce and Sherman 1999).

3.3.2.3. Exposure to 5 mg/L NP results in downregulation of genes associated with O-linked glycosylation

Two mannosyltransferase encoding genes (*MNN1* and *MNN5*) were downregulated after 120 min exposure time, while five mannosyltransferase encoding genes (*MNT3*, *MNT4*, *MNN10*, *KTR7*, and *PMT4*) were repressed after 180 min exposure interval. In the cell wall of *S. cerevisiae*, the glycoproteins are organized with N-linked and O-linked glycans. Of these, the O-linked structures contain 4-5 mannoses that are attached to serines and threonines. 40% of the dry weight of the cell wall occurs from

mannoproteins via mannan synthesis and these mannoproteins is believed to strengthen the structural integrity of the cell wall by formin an external layer to the wall (Jungmann et al. 1999). It was also showed that mutations causing deficiency in mannans result in synthetic lethality with protein kinase C pathway components regulating the expression of cell wall components (Neiman et al. 1997; Jungmann et al. 1999). Moreover, yeast cells must organize actin cytoskeleton properly and have a functional mitotic checkpoint to be able to survive without mannans (Jungmann et al. 1999). The downregulation of these genes suggests that high level of NP may cause defect in cell wall of yeast cells. Moreover, upregulation of other cell wall components which will be discussed in more depth in one of the subsequent sections supports this speculation.

3.3.2.4. Exposure to 5 mg/L NP results in downregulation of genes involved in cell cycle progression

In contrast to results obtained from BPA exposure, we observed that three cell cycle progression genes (*CLB1*, *CLB6*, and *CLN1*) were downregulated after 120 exposure time. In addition to *CLB1*, *CLB2* were also significantly downregulated after 180 min exposure. Cyclins activate cyclin-dependent kinases (CDKs) that are regulatory units involved in the regulation of the cell cycle progression which is conserved among eukaryotes. *CLN1* encodes G1 cyclin involved in regulation of the cell cycle and activates Cdc28p kinase to promote the G1 to S phase transition. *CLB1* and *CLB2* encode B-type cyclin involved in cell cycle progression and activates Cdc28p to promote the transition from G2 to M phase during the cell cycle. Transcripts of these genes accumulate during G2 and M phases and they are repressed at the end of mitosis (Fitch et al. 1992). *CLB6* encodes B-type cyclin involved in DNA replication during S phase and activates Cdc28p to promote initiation of DNA synthesis (Lew et al. 1997). This finding suggests that NP may inhibit cell cycle progression.

3.3.2.5. Exposure to 5 mg/L NP results in reduced expression of genes involved in ribosomal activity

As previously detailed, ribosomal biogenesis consists of a complex series of processes and a large number of ribosomes are needed for cell growth. Any deficiency in the regulation of this process may cause severe effects. In the present study, several genes

associated with ribosomal biogenesis including rRNA and nuclear RNA processing (five genes), RNA polymerase I subunits (three genes), ATP-dependent RNA helicase (two genes), ribosomal SSU and LSU biogenesis and related processes (13 genes) in *S. cerevisiae* upon exposure to 5 mg/L NP for 120 min. On the other hand, several different genes associated with ribosomal SSU (five genes) and LSU (two genes) except *RPL12A* which was repressed at both exposure time, were downregulated in *S. cerevisiae* in response to high inhibition concentration for 180 min. These findings conflict with that of previous observation obtained from *S. cerevisiae* exposed to BPA with several enhanced genes associated with ribosomal biogenesis.

3.3.2.6. NP may negatively affect peroxisome biogenesis

Three genes associated with peroxisome, *PEX25*-required for the regulation of peroxisome size and maintenance, *PEX31*- involved in negative regulation of peroxisome size, and *INP2*-required for peroxisome inheritance were repressed upon exposure to 5 mg/L NP for 120 min. Peroxisomes organize a wide variety of metabolic pathways playing roles in several processes, such as the regulation of cellular oxygen, inactivation of toxic substances, and the metabolism of lipids, nitrogen bases, and carbohydrates. They are required for proper human development and physiology, and abnormal assemble of peroxisomes is associated with a group of genetic disorders called the peroxisome biogenesis disorders (PBDs). Genes involved in peroxisome assembly are known as PEX genes and mutations in several human orthologs of these genes have been found to cause PBDs (Tam et al. 2003).

3.3.2.7. Exposure to high inhibition concentration of NP results in downregulation of mitochondrial biogenesis

Mitochondria are essential organelles for several cellular processes including energy production, metabolism, cellular proliferation, differentiation and cell death. To be able to carry out such processes, the morphology, numbers and distributions of mitochondria change in different cell types. The morphological organization of mitochondria is maintained and protected by regular cell fusion and division rates under normal conditions (Hermann et al. 1997; Zhang et al. 2014). Exposure to high inhibition concentration of NP for 120 min also affected mitochondrial distribution and

morphology genes. Two genes, *MDM20* (involved in mitochondrial inheritance and actin assembly) and *MDM36* (required for normal mitochondrial morphology and inheritance) were significantly downregulated.

Moreover, several genes associated with mitochondrial biogenesis were significantly affected by 5 mg/L NP exposure for 180 min. Similarly to BPA exposure, *TIM21* and *IMP2* encoding subunits of the TIM23 and peptidase complexes, respectively, which are essential components of the mitochondrial inner membrane were downregulated (Luo et al. 2006; van der Laan et al. 2006). Besides, *PET54*, *OAC1*, and *ARH1* were three downregulated genes encoding mitochondrial inner membrane protein that binds to the 5' UTR of the COX3 mRNA to activate its translation together with Pet122p and Pet494p (Costanzo et al. 1989), mitochondrial inner membrane transporter that transports oxaloacetate, sulfate, thiosulfate, and isopropylmalate (Palmieri et al. 1999), and oxidoreductase of the mitochondrial inner membrane which is involved in cytoplasmic and mitochondrial iron homeostasis (Li et al. 2001), respectively. Moreover, one mitochondrial GTP/GDP transporter encoding gene (*GGC1*), one mitochondrial translational activator of the COB mRNA encoding gene (*CBS1*), one mitochondrial elongation factor encoding gene (*MEF2*), one protein subunit of mitochondrial RNase P encoding gene (*RPM2*), one mitochondrial intermediate peptidase encoding gene (*OCT1*), one divalent metal ion transporter encoding gene (*SMF1*), one mitochondrial C1-tetrahydrofolate synthase encoding gene (*MIS1*), one mitochondrial serine hydroxymethyltransferase encoding gene (*SHM1*), one mitochondrial NADP-specific isocitrate dehydrogenase encoding gene (*IDP1*), one mitochondrial ribosomal protein of the small subunit encoding gene (*MRPS35*), and one mitochondrial ribosomal protein of the large subunit encoding gene (*RML2*) were significantly downregulated. We suggest that NP may affect mitochondrial biogenesis as evidenced by the downregulation of these essential components of the mitochondrial biogenesis, which mediates various functions in mitochondrion sub-compartments.

3.3.2.8. Exposure to 5 mg/L NP results in reduced expression of genes involved in oxidative phosphorylation (OXPHOS)

Several genes associated with the OXPHOS system, which includes five enzyme complexes (complex I to complex V) and two electron carriers (quinone-coenzyme Q

and cytochrome C) (Fernandez-Vizarra et al. 2009), were significantly downregulated in *S. cerevisiae* in response to exposure to 5 mg/L for 180 min. As previously described the OXPHOS converts substrates produced via glycolysis and β-oxidation into energy (ATP) and mitochondria play an active role in death and survival signaling pathways. In particular, many mitochondrial diseases and serious neurodegenerative diseases, such Parkinson's, Alzheimer's, and Huntington's disease, are linked to mitochondrial defects (Diaz 2010). In the present study, one gene (*SDH2*) associated with mitochondrial complex II [i.e., succinate dehydrogenase (SDH)], four genes (*QCR2, QCR7, QCR8*, and *QCR10*) associated with mitochondrial complex III, also known as ubiquinol cytochrome-c reductase or cytochrome bc1 complex, six genes (*COX4*, *COX6*, *COX7*, *COX12*, *COX13*, and *COX15*) associated with mitochondrial respiratory chain complex IV, referred to as cytochrome c oxidase (COX), and two genes (*ATP17* and *ATP25*) associated with complex V known as F_0F_1-ATP synthase were repressed. In addition to these genes, reduced expression of the protein that comprise cytochrome c, *CYC1*-cytochrome c isoform 1, the latter of which is associated with the electron carrier of the mitochondrial inner membrane (Gaignard et al., 2013), and *AFG1* which may act as a chaperone in the degradation of misfolded or unassembled cytochrome c oxidase (Khalimonchuk et al., 2007) subunits were also observed in response to the high NP concentration for 180 min.

3.3.2.9. NP inhibits the expression of de novo biosynthesis of NAD and pyrimidines

As observed in *S. cerevisiae* cells treated with low and high levels of BPA, two genes (*BNA1* and *BNA4*) required for the de novo biosynthesis of NAD from tryptophan via kynurenine were significantly downregulated upon exposure to high inhibition concentration of NP for 180 min. NAD is used as a cofactor for energy metabolism and as a substrate in several biological processes, such as signaling pathways, transcriptional regulation, DNA repair, age-associated diseases, and life span extension (Lin and Guarente, 2003).

Comprehensive information have been obtained about the de novo biosynthesis of pyrimidine pathway thanks to the studies performed on higher eukaryotes specifically mammalian cells. These studies have showed that the de novo biosynthesis of pyrimidine nucleotides are essential precursors for growth-related processes. For

instance, the uracil and cytosine nucleotides are necessary for the synthesis of RNA, DNA, phospholipids, UDP sugars and glycogen. Moreover, it has been indicated that some synthetic pyrimidine enzymes have higher activities in tumor cells and several studies have been conducted to design inhibitors of pyrimidine synthesis that resulted in useful drugs for the treatment of leukemia and different cancer types (Huang and Graves, 2003). Three genes (*URA1*, *URA4*, and *URA5*) associated with de novo biosynthesis of pyrimidines were significantly repressed in *S. cerevisiae* in response to high levels of NP after 180 min. *URA1* encodes dihydroorotic acid dehydrogenase which catalyzes the fourth enzymatic step in the de novo biosynthesis of pyrimidines (Vorisek et al. 2002). It has been shown that the expression of *URA1* is repressed by chemicals, DMSO and lithium (Bro et al. 2003; Zhang et al. 2003). *URA4* encodes dihydroorotase which catalyzes the third step in the de novo biosynthesis of pyrimidines (Guyonvarch et al. 1988), while *URA5* encodes orotate phosphoribosyltransferase isozyme that catalyzes the fifth enzymatic step in this pathway (de Montigny et al. 1989). It has been found that mutations in the human homolog of this gene result in orotic aciduria which is a human disease of the de novo pyrimidine biosynthetic pathway (Suchi et al. 1997). In addition to these genes, two genes (*FUI1* and *FUR4*) encode uridine permease and uracil permease, respectively were also repressed.

3.3.2.10. NP may suppress RNA polymerase II-mediated transcription

One subunit of TFIIE (*TFA2*) and two subunits of TFIIH (*TFB2* and *TFB4*) which are involved in RNA polymerase II transcription initiation were downregulated upon exposure to NP for 180 min.. *TFA2*, small subunit of TFIIE, is involved in RNA polymerase II transcription initiation and required for cell viability (Feaver et al. 1994). On the other hand, *TFB2*, subunit of TFIIH, is associated with transcription initiation and required for nucleotide excision repair, while *TFB4*, another subunit of TFIIH, is also involved in transcription initiation and similar to 34 kDa subunit of human TFIIH (Feaver et al. 1997; Prakash and Prakash 2000). In contrast to this observation, as mentioned above, upregulation of two important subunits of TFIID and TFIIF upon exposure to BPA was detected.

3.3.2.11. Exposure to 5 mg/L NP results in downregulation of genes associated with N-linked glycosylation

Three genes (*ALG5*, *ALG7*, and *ALG13*) associated with the dolichol pathway of protein asparagine-linked glycosylation were significantly downregulated upon exposure to NP for 180 min. The synthesis of oligosaccharides via N-linked glycosylation of proteins occurs with several steps carried in the endoplasmic reticulum and the Golgi. The high-mannose core oligosaccharides are assembled on the dolichyl pyrophosphate with two molecules of N-acetylglucosamine (GlcNAc), nine molecules of mannose, and three molecules of glucose. Then, these oligosaccharide cores are transferred to asparagine residues in the endoplasmic reticulum. Subsequently, the oligosaccharide cores are modified in the Golgi apparatus and various glycosylated proteins are generated (Barnes et al. 1984). In this process, *ALG5* encodes dolichyl-phosphate glucosyltransferase involved in asparagine-linked glycosylation in the endoplasmic reticulum (Stagljar et al. 1998), while *ALG7* encodes UDP-N-acetyl-glucosamine-1-P transferase involved in catalyzation the first step in the synthesis of lipid-linked oligosaccharides and addition of the first N-acetylglucosamine to dolichyl phosphate on the cytosolic side of the endoplasmic reticulum (Barnes et al. 1984). Moreover, *ALG13* encodes a catalytic component of UDP-GlcNAc transferase required for the second step of dolichyl-linked oligosaccharide synthesis (Gao et al. 2005).

Meanwhile, the majority of the genes that were upregulated in response to high inhibition concentration of NP were associated with response to chemical, carbohydrate metabolic process, transcription from RNA polymerase II promoter, cell wall organization or biogenesis, transmembrane and ion transport in both exposure times (Table 3.11). Each of these functions is discussed in more depth in following sections.

Table 3.11 Selected biological processes significantly enriched among the genes upregulated in *S. cerevisiae* cells exposed to 5 mg/L nonylphenol (NP) for 120 and 180 minutes

120 minutes exposure			
GOID	**GO term**	**Frequency**	**Gene(s)**
42221	response to chemical	48/510 genes 9.4%	*PDR3*, *UGA2*, *NRG2*, *TPS1*, *HSP30*, *FIG2*, *RPN4*, *HBT1*, *UBC1*, *CTA1*, *PDR15*, *TSA2*, *MFA1*, *FRD1*, *HSP12*, *HAC1*, *AGA2*, *MIG2*, *STF2*, *MTL1*, *NQM1*, *SLI1*, *VMR1*, *BAR1*, *VHR1*, *XBP1*, *IML2*, *SIP4*, *GPX1*, *HSP104*, *FET3*, *GAD1*, *SIP18*, *CRZ1*, *NCE103*, *MFA2*, *PDR16*, *BXI1*, *DDR2*, *TMC1*, *GCY1*, *PDR5*, *PDR10*, *POS5*, *USV1*, *RDS3*, *YDL124W*, *YJL144W*
5975	carbohydrate metabolic process	37/510 genes 7.3%	*GAL7*, *GAL10*, *TPS1*, *GID7*, *GLK1*, *CIT2*, *NDE2*, *TPS2*, *GLC3*, *UBC8*, *GIP2*, *IGD1*, *PYC1*, *AMS1*, *TOS3*, *PIG2*, *SGA1*, *GUT2*, *IMA3*, *SIP4*, *INO1*, *FBP26*, *PCK1*, *HSP104*, *XYL2*, *GAL2*, *FBP1*, *TSL1*, *SRT1*, *PGM2*, *CRZ1*, *MLS1*, *GCY1*, *GAC1*, *TYE7*, *YIG1*, *GDB1*

Table 3.11 continued

6366	transcription from RNA polymerase II promoter	24/510 genes 4.7%	*PAU8*, *PDR3*, *NRG2*, *RPN4*, *REF2*, *CRF1*, *MET32*, *YAP6*, *EMI2*, *HAC1*, *HSF1*, *MIG2*, *RTF1*, *NDT80*, *VHR1*, *XBP1*, *SIP4*, *TAF11*, *CRZ1*, *GAL11*, *SKM1*, *USV1*, *CSR2*, *YHR177W*
55085	transmembrane transport	22/510 genes 4.3%	*PEX22*, *RTC2*, *FTH1*, *SUL1*, *PHO89*, *VBA3*, *ADY2*, *GPD1*, *CCC2*, *ATO3*, *SIT1*, *HXT13*, *SSA4*, *FTR1*, *PEX21*, *MPC3*, *FET3*, *TOM7*, *SKM1*, *PDR10*, *YFL040W*, *YOL162W*
71554	cell wall organization or biogenesis	22/510 genes 4.3%	*TIP1*, *FMP45*, *DIT1*, *SPS2*, *SPS1*, *SHE10*, *MTL1*, *SPS100*, *SDP1*, *YPS6*, *PIR3*, *PIR1*, *OSW2*, *CRZ1*, *YGP1*, *LDS2*, *GAS4*, *HPF1*, *PTP2*, *OSW1*, *CSR2*, *YLR194C*
6811	ion transport	22/510 genes 4.3%	*RTC2*, *FTH1*, *SUL1*, *PHO89*, *VBA3*, *ADY2*, *CCC2*, *ATO3*, *FTR1*, *BTN2*, *MPC3*, *SFC1*, *GAP1*, *CTR3*, *FET3*, *CRZ1*, *PDR16*, *ENB1*, *RSB1*, *COT1*, *DIP5*, *CTR1*

Table 3.11 continued

180 minutes exposure			
42221	response to chemical	50/473 genes 10.6%	*PDR3*, *UGA2*, *NRG2*, *HSP30*, *FIG2*, *RPN4*, *HBT1*, *SNQ2*, *UBC1*, *CTA1*, *PDR15*, *TSA2*, *MFA1*, *FRD1*, *MIG3*, *UBC6*, *HSP12*, *GAT1*, *AGA2*, *MIG2*, *MTL1*, *NQM1*, *SLI1*, *VMR1*, *YHK8*, *SCH9*, *BAR1*, *VHR1*, *XBP1*, *IML2*, *SIP4*, *IXR1*, *HSP104*, *AFB1*, *YAP1*, *FET3*, *SIP18*, *CRZ1*, *NCE103*, *MLF3*, *MFA2*, *PDR16*, *AGA1*, *DDR2*, *PDR5*, *PDR10*, *USV1*, *RDS3*, *YDL124W*, *YJL144W*
6366	transcription from RNA polymerase II promoter	42/473 genes 8.9%	*PAU8*, *PDR3*, *TOD6*, *NRG2*, *RPN4*, *REF2*, *MET32*, *EMI2*, *MIG3*, *ACA1*, *RPH1*, *GAT1*, *PHO4*, *AFT1*, *HSF1*, *MIG2*, *RTF1*, *TFG2*, *NDT80*, *SCH9*, *VHR1*, *XBP1*, *SIP4*, *IME1*, *IXR1*, *ABF1*, *YAP1*, *TAF11*, *MCM1*, *RGM1*, *CRZ1*, *MKS1*, *RAP1*, *NRD1*, *GAL11*, *SDH5*, *RLM1*, *USV1*, *CSR2*, *ROX1*, *YHR177W*, *YOR338W*

Table 3.11 continued

5975	carbohydrate metabolic process	27/473 genes 5.7%	*GAL7*, *VID24*, *GID7*, *NDE2*, *PMT5*, *UBC8*, *IGD1*, *AMS1*, *TOS3*, *CRH1*, *SGA1*, *GUT2*, *SIP4*, *INO1*, *PCK1*, *XYL2*, *GAL2*, *FBP1*, *SRT1*, *CRZ1*, *RAP1*, *GPD2*, *GAC1*, *TYE7*, *HSP104*, *YIG1*, *GDB1*
6811	ion transport	26/473 genes 5.5%	*RTC2*, *FTH1*, *PHO89*, *VBA3*, *ADY2*, *CCC2*, *ATO3*, *FTR1*, *FET5*, *AFT1*, *BTN2*, *MPC3*, *SFC1*, *GAP1*, *FRE1*, *CTR3*, *FET3*, *CRZ1*, *PDR16*, *FRE7*, *ENB1*, *RSB1*, *MCH5*, *COT1*, *DIP5*, *CTR1*
71554	cell wall organization or biogenesis	23/473 genes 4.9%	*TIP1*, *FMP45*, *PST1*, *DIT2*, *DIT1*, *SPS1*, *SHE10*, *MTL1*, *CRH1*, *SPS100*, *IRC18*, *HSP150*, *PIR3*, *PIR1*, *YLR194C*, *CRR1*, *CCW14*, *CRZ1*, *YGP1*, *LDS2*, *HPF1*, *PTP2*, *CSR2*
55085	transmembrane transport	20/473 genes 4.2%	*PEX22*, *RTC2*, *FTH1*, *PHO89*, *VBA3*, *ADY2*, *CCC2*, *ATO3*, *SIT1*, *HXT13*, *SSA4*, *FTR1*, *TOM20*, *PEX21*, *MPC3*, *HOT13*, *AQY2*, *FET3*, *YOL162W*, *PDR10*

3.3.2.12. Exposure to 5 mg/L NP results in enhanced expression of genes encoding heat shock proteins and ubiquitin-conjugating enzymes

Several genes encoding heat shock proteins (HSPs) were significantly upregulated in *S. cerevisiae* in response to high inhibition concentration of NP for both 120 and 180 exposure times. HSPs are involved in respond to various environmental stresses and conserved during the evolution. Several HSPs that have structural resemblance but functional differences are found among organisms. Along with the activity against negative effects of stresses, HSPs are essential under normal conditions, particularly in the biogenesis of proteins from the synthesis of first chain to the formation of multimeric complexes, and therefore they are called as molecular chaperones (Craig et al. 1993; Becker and Craig 1994). In the case of the formation of unfolded and/or nonfunctional proteins during abnormal cellular processes, molecular chaperones may aid proteins in refolding to their native structure or in proteolysis (Craig et al. 1993). Seven genes (*HSP12*, *HSP30*, *HSP42*, *HSP78*, *HSP104*, *HSF1*, and *SSA4*) were induced at both exposure times. Moreover, *SSE2* which is a member of Hsp110 subclass of the heat shock protein 70 (HSP70) family was only induced upon exposure for 120 min. It serves as nucleotide exchange factor to load ATP onto the SSA class of cytosolic Hsp70s which are known to serve as molecular chaperones, binding newly-translated proteins to assist in proper folding and prevent aggregation/misfolding (Becker and Craig 1994). On the other hand, *HSP150* and *MDJ1* were two genes induced upon exposure for 180 min. *HSP150* encodes O-mannosylated heat shock protein and is required for cell wall stability (Moukadiri and Zueco 2001). MDJ1 encodes co-chaperone that stimulates HSP70 protein Ssc1p ATPase activity and is involved in protein folding/refolding in the mitochodrial matrix (Westermann et al. 1996). Several studies showed enhanced expression of genes encoding heat shock proteins in response to various stresses. Alexandre et al., (2001) found that genes encoding heat shock proteins were upregulated in response to ethanol stress. Moreover, it was reported that the expression of the genes *HSP70* and *HSP90* was significantly induced in *C. japonica* crabs exposed to different concentration of NP (Park and Kwak, 2013; Park and Kwak, 2014). In yeast cells in response to cadmium, several stress genes including *HSP12* and *HSP26* were significanlty upregulated (Momose and Iwahashi, 2001).

We also detected significant upregulation of several genes encoding ubiquitin-conjugating enzymes which are conserved among eukaryotes and play central roles in cellular stress response, degradation of short-lived and abnormal proteins (Jentsch et al. 1987; Hiraishi et al. 2006). *UBC1*, *UBC6*, *UBC8*, *UBI4*, and *PSH1* were induced upon exposure to 5 mg/L NP for 180 min. Of these, *UBC1*, *UBC8*, and *UBI4* were also upregulated after 120 min exposure time. It was showed that *UBI4* transcription increases in response to a wide variety of stress treatments including heat shock, DNA-damaging agents, such as 4 nitroquinoline-1-oxide (4NQO) and methyl methane sulphonate (MMS), and inhibitors of DNA replication, such as hydroxyurea, amino-acid analogues and heavy metals (Finley et al. 1987; Treger et al. 1988; Simon et al. 1999). Moreover, it was indicated that environmental stresses applied to *S. cerevisiae* cells result in protein degradation and abnormal proteins that cause growth inhibition and also cell death (Hiraishi et al. 2006). Taking together, we speculated that increased expression of genes encoding molecular chaperones and ubiquitin-conjugating enzymes, and also inhibition in cell growth indicate that NP exposure may cause cellular stress leading abnormal and/or nonfunctional proteins.

3.3.2.13. Exposure to the high inhibition concentration of NP promotes the expression of genes involved in iron and copper acquisition

Similar to low levels of NP exposure, in both exposure time to high inhibition concentration of NP, several genes associated with iron and copper acquisition were significantly induced. *FET3*, *FTH1*, *FTR1*, and *SIT1* were common upregulated genes associated with iron acquisition, while *CTR1*, *CTR3*, *CCC2*, and *SIT1* were the common genes involved in copper acquisition at both exposure times. In addition to these genes, two genes associated with iron uptake (*FRE1* and *FRE7*), one ferric enterobactin transporting gene (*ENB1*), and two genes (*AFT1* and *FET5*) involved in transcriptional regulation of ferric reductase were the genes induced after180 min exposure. This finding with that of previous observations from 1 mg/L NP exposure suggest that NP may prevent iron and copper uptake by cells or interfere with these ions indirectly, thereby reducing nutrient allocation to the appropriate compartments as we indicated for BPA data.

3.3.2.14. Exposure to a high inhibition concentration of NP results in upregulation of chemical-response genes

As observed in *S. cerevisiae* cells treated with BPA and exposed to low levels of NP for 120 min, several genes encoding transporters of the ABC superfamily were significantly induced upon exposure to high inhibition concentration of NP for 120 and 180 min. *PDR3*, *PDR5*, *PDR10*, *PDR15*, and *PDR16* were upregulated at both exposure times to 5 mg/L NP. Besides, *SNQ2* and *VMR1* were other genes induced after 180 min exposure. These findings indicate that both low and high levels of NP may trigger PDR network in yeast cells which suggests that certain gene products induced in the present study may aid in protecting yeast cells against NP exposure by pumping NP molecules out of the cytoplasm as we speculated for BPA data.

3.3.2.15. Exposure to 5 mg/L NP results in increased expression of genes involved in sugar and glycogen metabolisms

Sugar metabolism appeared to be significantly affected by exposure to high inhibition concentration of NP, as evidenced by upregulation of several hexose transporter genes. *HXT1*, *HXT2*, *HXT5*, and *HXT13* were induced upon exposure for both 120 and 180 min. Of these, *HXT2* and *HXT13* encode high-affinity hexose transporters, while *HXT5* encodes a moderate hexose transporter (Özcan and Johnston 1999). Besides, *HXT9*, *HXT11*, and *HXT14* were upregulated in *S. cerevisiae* in response to 5 mg/L NP after 120 min. Of these *HXT9* and *HXT11* are known as MSF related genes and *HXT14* encodes a high-affinity hexose transporter (Özcan and Johnston 1999). Moreover, four of these genes (*HXT1*, *HXT11*, *HXT13*, and *HXT15*) were downregulated upon exposure to low inhibition concentration of NP which suggests that increasing of NP concentration may change the regulation of these genes in yeast cells and need for glucose may change in the opposite manner comparing with the effect of low inhibition concentration. Genes involved in galactose metabolism were also affected in yeast cells in response to 5 mg/L NP. *GAL2*, *GAL7*, *GAL10*, and *GAL11* were induced upon exposure to NP for 120 min. Of these, *GAL2*, *GAL7*, and *GAL11* were also induced after 180 min exposure to NP. *GAL2* encodes a high affinity galactose permease which is an integral plasma membrane protein belonging to a superfamily of sugar transporters, required for utilization of galactose, and able to transport glucose (Tschopp et al. 1986).

GAL7 encodes Gal7p galactose-1-phosphate uridylyltransferase that catalyzes the conversion of galactose-1-phosphate to UDP-galactose and mutations in human ortholog GALT have been linked to lethal disease galactosemia (Christacos et al. 2000). *GAL10* encodes a bifunctional enzyme with mutarotase and UDP galactose 4-epimerase activities and human homolog GALE is also implicated in galactosemia (Majumdar et al. 2004; McCorvie et al. 2012).

As observed for the low inhibition concentration group, several genes involved in glycogen metabolic process were upregulated in *S. cerevisiae* cells exposed to 5 mg/L NP. Six genes (*GIP2*, *PIG2*, *GDB1*, *GAC1*, *IGD1*, and *GLC3*) were significantly affected upon exposure for 120 min and three of these genes (*GDB1*, *GAC1*, and *IGD1*) were also induced after 180 min exposure.

3.3.2.16. NP induces the expression of autophagy-related genes

As observed in *S. cerevisiae* cells treated with low inhibition concentration of NP, several autophagy-related genes were significantly upregulated upon exposure to 5 mg/L of NP. *ATG8*, *ATG10*, and *ATG41* were affected after both 120 and 180 min exposure, while *ATG34* was induced only after 120 min exposure and *ATG1* was upregulated after 180 min exposure. As it was indicated earlier, this observation conflicts with the result obtained from BPA treatment which repressed genes involved in autophagy.

3.3.2.17. Exposure to high inhibition concentration of NP may promote cell wall biogenesis

Several genes encoding cell wall proteins were significantly affected upon exposure to 5 mg/L NP. Six genes (*TIP1*, *FIG2*, *PAU24*, *YGP1*, *PIR1*, and *PIR3*) were induced after both exposure times. *TIP1* encodes a major cell wall mannoprotein which is induced by heat- and cold-shock (Kondo and Inouye 1991), while *PAU24* encodes cell wall mannoprotein and is expressed under anaerobic conditions and repressed during aerobic growth (Luo and van Vuuren 2009). *FIG2* encodes a cell wall adhesion which is thought to be required for maintenance of cell wall integrity during mating (Zhang et al. 2002). *YGP1* encodes a cell wall-related secretory glycoprotein and is upregulated by nutrient deprivation-associated growth arrest (Destruelle et al. 1994). *PIR1* and *PIR3*

encode O-glycosylated covalently-bound cell wall proteins and are required for cell wall stability (Mrsa and Tanner 1999). *NCW2* which encodes a structural constituent of the cell wall and is attached to the plasma membrane by a GPI-anchor was induced after 120 min exposure to NP. It was showed that *NCW2* plays role in cell wall biogenesis and the expression of this gene is induced in response to cell wall stress (Terashima et al. 2000; Elsztein et al. 2016). On the other hand, *PST1* and *CCW14* were upregulated after 180 min exposure. *PST1* encodes a cell wall protein and is induced by cell wall damage (Terashima et al. 2000), while *CCW14* encodes a covalently linked cell wall glycoprotein and is found in the inner layer of the cell wall (Mrsa et al. 1999). Moreover, various genes associated with cell wall were induced in response to high levels of NP. *BAG7* and *ARC18* were affected after both 120 and 180 min exposure times. *BAG7* act as a Rho GTPase activating protein that plays a central role in regulating of cell wall synthesis and organization of the actin cytoskeleton. It has been shown that highly upregulation of *BAG7* suppresses the lethality of *RHO1* hyperactivation in response to cell wall damage (Schmidt et al. 2002). *ARC18* encodes a subunit of the ARP2/3 complex and null mutant of this gene cannot localize actin patches to growing buds and shows defect in cell growth and vability (Winter et al. 1999). Besides, *YPK2* which was induced after 120 min exposure to NP, encodes a protein kinase participating in a signaling pathway required for optimal cell wall integrity (Roelants et al. 2002). In addition, *CRH1*, a gene encoding a glycosylphosphatidylinositol-cell wall protein involved in adaptation of cell wall stress, was significantly induced upon exposure to NP for 180 min. (Bermejo et al. 2008). Agarwal et al. (2003) reported that yeast cells respond to amphotericin B and caspofungin by inducing several genes involved in cell wall maintenance and integrity, and suggested that increased expression of these genes exhibits a compensatory reaction to cell wall damage and an increase of strength in cell wall. Taking together, these data suggest that high inhibition concentration of NP may damage the cell wall and yeast cells upregulate many genes encoding cell wall proteins and functioning in cell wall biosynthesis to overcome this possible NP toxicity.

3.3.2.18. High inhibition concentration of NP upregulates the expression of genes encoding aldehyde dehydrogenases

Aldehyde dehydrogenases have an essential role in metabolic pathways, particularly in the conversion of acetaldehyde to acetyl-CoA during growth on non-fermentable carbon sources and also in the detoxification of toxic chemical intermediates accumulated under stress conditions (Aranda and del Olmo 2003). Mutations in human aldehyde dehydrogenase genes are associated with various metabolic disorders such as alcoholism and carcinogenesis. (Navarro-Avino et al. 1999). We found that two genes (*ALD3* and *ALD6*) encoding cytosolic aldehyde dehydrogenase and one gene (*ALD4*) encoding mitochondrial aldehyde dehydrogenase were significantly upregulated upon exposure for 120 min to 5 mg/L NP. Of these, *ALD4* and *ALD6* were also induced after 180 min exposure. This finding suggests that high inhibition concentration of NP may result in accumulation of some harmful chemical intermediates or may be detected as toxic chemical by yeast cells and cells upregulates these genes to remove such intermediates.

3.3.2.19. Exposure to the high inhibition concentration of NP results in upregulation of genes associated with ribonucleotide reductase (RNR)

RNR, a tetrameric protein complex, catalyzes the conversion of ribonucleotides to deoxyribonucleotides in de novo deoxyribonucleotide biosynthesis. RNR has a central role in regulating the overall and balance concentrations of dNTPs for an accurate genome duplication. It also plays an essential role in high-fidelity DNA replication and DNA repair processes (Huang and Elledge 1997; Perlstein et al. 2005). RNR complex is composed of two small subunits (Rnr2p and Rnr4p) and two large subunits (Rnr1p and Rnr3p). In case of deficiency in S phase and/or DNA damage during the cell cycle progress, transcripts encoding Rnr2p:Rnr4p subcomplex are highly induced and the subcomplex binds the Rnr1p homodimer to form an active RNR (Huang and Elledge 1997; Yao et al. 2003). It was indicated that RNR may be a good target for cancer therapy, because the assembly of RNR and translation of *RNR2* may lead increase tolerance to DNA damage agents and the overexpression of *RNR2* may protect cells from chemotherapeutic drugs (Abid et al. 1999). Moreover, the small subunit of RNR complex is found as action site for antitumor agents in mammalian cells (Rittberg and

wright 1989). We found several induced genes related to RNR complex in *S. cerevisiae* exposed to high inhibition concentration of NP. *RNR2*, *RNR3*, *RNR4*, and *HUG1* were upregulated after 120 min exposure. Of these, *RNR2*, *RNR3*, and *HUG1* were also upregulated after 180 min exposure. Based on these results, we speculate that NP may cause DNA damage during cell cycle and yeast cells respond to this effect by upregulating RNR complex related genes.

3.3.2.20. Exposure to the high inhibition concentration of NP results in enhanced expression of genes involved in trehalose biosynthesis

Biosynthesis of trehalose occurs in two steps. In the first step, glucose 6-phosphate and UDP-glucose are converted to alpha,alpha-trehalose 6-phosphate by trehalose-6-phosphate synthase (TPS) that encoded by *TPS1*. In the second step, trehalose-6-phosphate phosphatase (TPP), encoded by *TPS2*, converts alpha,alpha-trehalose 6-phosphate into trehalose and phosphate (François and Parrou, 2001). Four genes associated with trehalose biosynthesis (*TPS1*, *TPS2*, *TSL1*, and *PGM2*) were significantly induced upon exposure to high inhibition concentration of NP for 120 min, while none of these genes or any genes related to trehalose were affected after 180 min. In yeast cells, trehalose is the primary storage carbohydrate in response to various stresses, such as thermal, osmotic, oxidative, and ethanol (Pereira et al., 2001). Moreover, similar to our findings, it was reported that co-induction of the genes involved in trehalose synthesis with HSP genes in response to ethanol stress supports a strong connection between these genes (Alexandre et al., 2001). In addition, Liu and Sung, (2011) showed that the expression of a stress-related gene encoding TPS was significanlty upregulated in aquatic crustaceans in response to NP.

3.3.2.21. Exposure to the 5 mg/L NP promotes the expression of genes involved ribosomal biogenesis and RNA processing

Several genes involved in ribosomal biogenesis and RNA processing were significantly upregulated after 180 min exposure to 5 mg/L NP. Eight genes (*MRD1*, *IMP3*, *IMP4*, *KRI1*, *RCL1*, *SRP40*, *HCA4*, and *TSR4*) involved in ribosomal SSU, six genes (*MAK16*, *CIC1*, *NOP16*, *NOG1*, *RRS1*, and *RRP36*) associated with ribosomal LSU, two genes (*TOD6* and *MTR4*) associated with RNA processing were affected. Interestingly, as

indicated above, we also found that several genes associated with ribosomal biogenesis were downregulated upon exposure to high inhibition concentration of NP. In analyzing the process, it was observed that both the repressed and induced genes are involved in similar compartments of the process. Taken together, we speculated that ribosomal production of yeast cells may be affected by NP exposure and cells try to balance the production by downregulating and upregulating different genes of pathway.

3.3.3. Comparison of low and high inhibition concentrations of NP

Clustering analyses showed that several processes/pathways were significantly affected by both concentrations of NP. After 120 min treatment; the highly repressed genes in the 1 mg/L NP group were associated with cellular amino acid and monocarboxylic acid metabolic processes, ion transport, transmembrane transport, and transcription from RNA polymerase II promoter. Of these, monocarboxylic acid metabolic processes and transcription from RNA polymerase II promoter were not affected by high inhibition concentration group. On the other hand, exposure to 5 mg/L NP resulted in repression of genes associated with rRNA processing, mitotic cell cycle, and ribosomal small subunit biogenesis which were not affected by the 1 mg/L NP, and also transmembrane transport, cellular amino acid metabolic process, and ion transport. Among these affected processes, rRNA processing was the most repressed biological process with 16 genes upon exposure to 5 mg/L NP while monocarboxylic acid metabolic process was the least affected process with four genes and found in the 1 mg/L NP group (Figure 3.8). Moreover, functional annotations showed that genes involved in sugar transport, amino acid biosynthesis, zinc regulation, and phosphate metabolism were significanlty affected by low inhibition concentration group, while the affected genes were found in the 12-spanner drug:H(+) antiporter DHA1 family, O-linked glycosylation, cell cycle progression and ribosomal biogenesis upon exposure to 5 mg/L NP.

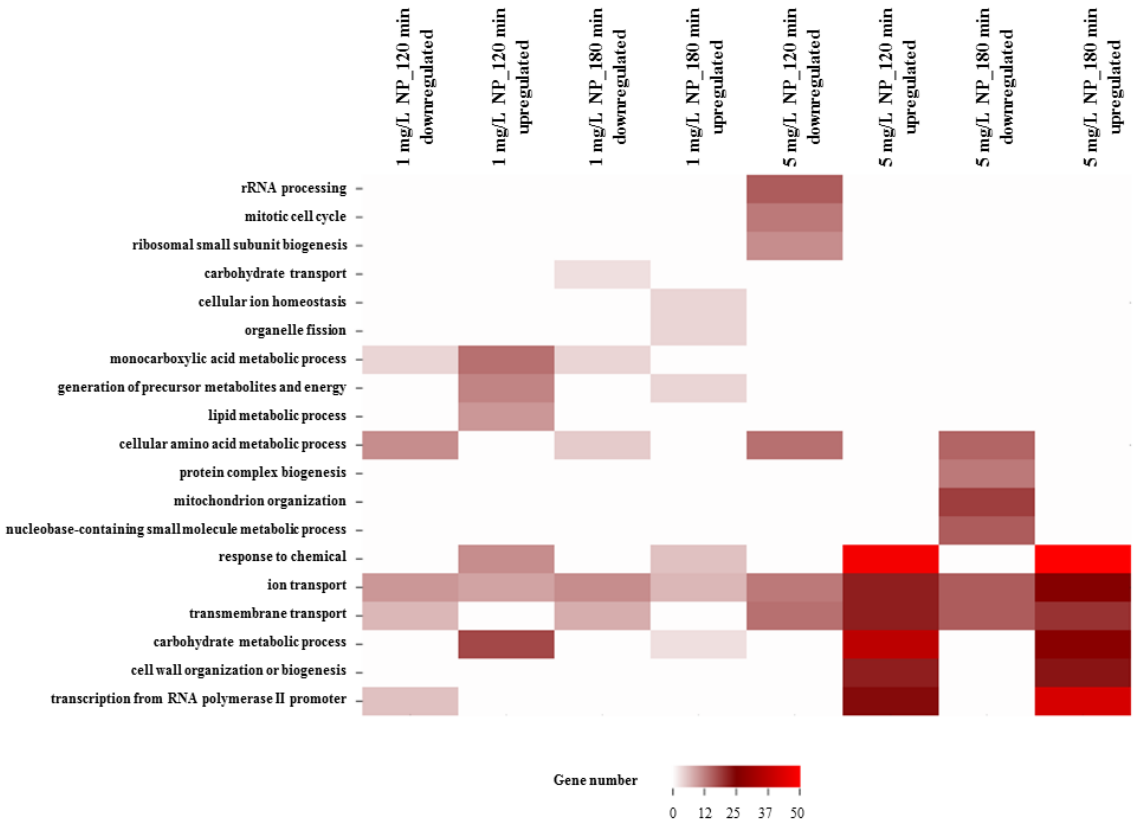


Figure 3.8 Comparison of the significantly enriched biological processes between 1 and 5 mg/L NP exposure

Conversely, the genes induced upon exposure to 1 mg/L NP were primarily associated with metabolic processes including carbohydrate, monocarboxylic acid, and lipid metabolic processes, generation of precursor metabolities and energy, response to chemical and ion transport. Of these, monocarboxylic acid and lipid metabolic processes, and generation of precursor metabolities and energy were not significantly affected by 5 mg/L NP. On the other hand, response to chemical, carbohydrate metabolic process, transcription from RNA polymerase II promoter, transmembrane transport, cell wall organization or biogenesis, and ion transport were the most induced processes upon exposure to high inhibition concentration of NP. Heat map analysis showed that cell wall organization or biogenesis, transmembrane transport, and transcription from RNA polymerase II promoter were the processes distinctively affected in the high inhibition group. Within these processes, ion transport was the least induced process with nine genes upon exposure to low inhibition concentration of NP, and response to chemical was the most induced biological process with 48 genes and

found in the high inhibition concentration group (Figure 3.8). Moreover, functional annotation for pathway analysis showed that genes involved iron and copper acquisition and autophagy were induced by both concentrations, while fatty acid metabolism, glycogen metabolic process, drug resistance, and maltose related genes were affected upon exposure to 1 mg/L NP. On the other hand, genes encoding molecular chaperones, cell wall biogenesis, ribonucleotide reductases, and trehalose biosynthesis were upregulated upon exposure to high inhibition concentration group.

After 180 min treatment; the most prominently repressed genes in the 1 mg/L NP group were involved in cellular amino acid and monocarboxylic acid metabolic processes, and transport processes such as ion, transmembrane, and carbohydrate transports. Within these processes, carbohydrate transport and monocarboxylic acid metabolic processes were specific to low inhibition concentration group. On the other hand, exposure to 5 mg/L NP resulted in reduced expression of genes associated with mitochondrion organization, transmembrane and ion transports, nucleobase-containing small molecule and cellular amino acid metabolic processes, and protein complex biogenesis. Of these, mitochondrion organization, nucleobase-containing small molecule, and protein complex biogenesis were not significantly affected by the 1 mg/L NP group. Among these affected processes, mitochondrion organization was the most repressed biological process with 19 genes upon exposure to 5 mg/L NP while carbohydrate transport was the least affected process with three genes and found in the 1 mg/L NP group (Figure 3.8). According to functional annotations, genes involved in sugar transport, aromatic amino acid biosynthesis, zinc regulation, and phosphate metabolism were significanlty downregulated in low inhibition concentarion group, while genes related to O-linked and N-linked glycosylation, mitochondrial biogenesis, OXPHOS, de novo biosynthesis of NAD and pyrimidines, RNA polymerase II-mediated transcription, and ribosomal activity were prominently induced in the 5 mg/L NP group. Besides, genes associated with the 12-spanner drug:H(+) antiporter DHA1 family were affected within both groups.

Considering the upregulated genes, ion transport, response to chemical, generation of precursor metabolities and energy, organelle fision, cellular ion homeostasis, and carbohydrate metabolic process were the processes affected upon exposure to 1 mg/L NP. Of these, cellular ion homeostasis, organelle fision, and generation of precursor

metabolities and energy were significantly affected processes in the 1 mg/L NP group compared with high level group. On the other hand, exposure to 5 mg/L NP induced genes involved in response to chemical, transcription from RNA polymerase II promoter, carbohydrate metabolic process, ion transport, cell wall organization or biogenesis, and transmembrane transport. Of these, transcription from RNA polymerase II promoter, cell wall organization or biogenesis, and transmembrane transport were significantly affected processes in the 5 mg/L NP group compared with low level group. Among all these processes, carbohydrate metabolic process was the least induced process with three genes upon exposure to low inhibition concentration of NP, and response to chemical was the most induced biological process with 50 genes and found in the high inhibition concentration group (Figure 3.8). Iron and copper acquisition was the common pathway affected while arginine catabolism was affected upon exposure to 1 mg/L NP and heat shock proteins, ubiquition-conjugating enzymes, cell wall biogenesis, drug resistance genes, ribosomal biogenesis and RNA processing were affected in high level group.

Although certain processes were affected by both concentrations, including ion transport, response to chemical, transmembrane transport, cellular amino acid and carbohydrate metabolic processes, there were several processes prominently affected depending upon the concentration. Moreover, the number and magnitude of the affected genes were also distinct for each concentration. After 5 mg/L NP exposure, there were severe effects on various processes and several genes, with substantial changes in expression. Meanwhile, 1 mg/L NP exposure resulted in more modest changes in expression of small number of genes. Besides, considering 120 min exposure time, there were only 15 common genes between downregulated genes of the low and high inhibition concentrations, while there were 63 common genes between upregulated genes of 1 mg/L and 5 mg/L NP treatments (Figure 3.9). Some of these genes were clustered within the common biological processes, while most of them were unrelated. On the other hand, after 180 min exposure time, there were 16 common genes between downregulated genes of the low and high inhibition concentrations, while there were only 31 common genes between upregulated genes of 1 mg/L and 5 mg/L NP treatments. Similarly to 120 min treatment, most of these genes were unrelated while a small number of them were found in the common biological processes. These results

demonstrate that yeast cells respond to NP in a concentration dependent manner.

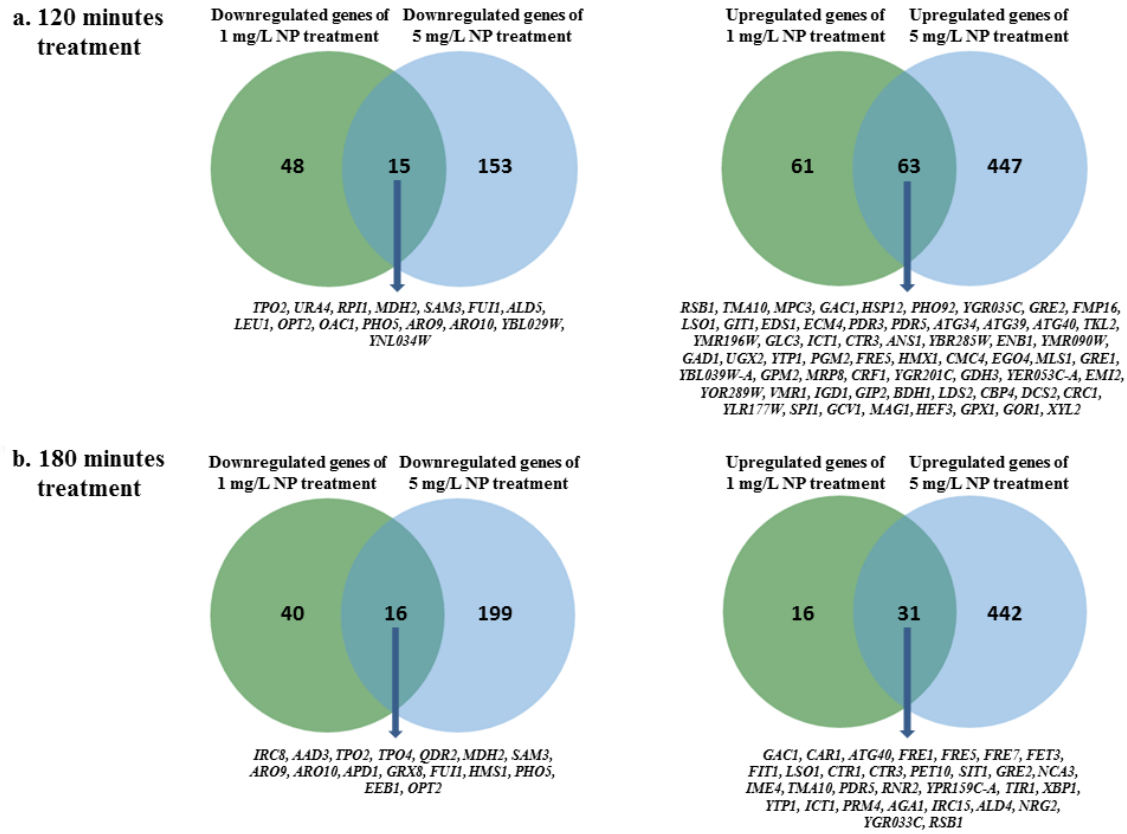


Figure 3.9 Common downregulated and upregulated genes upon exposure to 1 mg/L and 5 mg/L NP for 120 and 180 min

3.3.4. Validation of microarray data of NP by quantitative real-time RT-PCR analysis

qRT-PCR analysis was performed with the RNA samples used in the microarray experiments to validate the transcriptomic analyses results. For this purpose, 10 *S. cerevisiae* genes which repressed or induced upon exposure to the 5 mg/L NP for 180 min were selected. These genes were chosen to be included in a statistically significantly overrepresented biological process and/or to exhibit substantial changes in expression based on the microarray data. Of these 10 genes, three were downregulated (*QCR2*, *QCR7*, and *COX4*, which are involved in the OXPHOS system) and seven were upregulated [*PDR5*, *PDR16* and *SNQ2*, ABC superfamily; *FRE1* and *CTR3*, iron and copper acquisition; *SUE1*, protein involved in degradation of unstable forms of

cytochrome c; and *PHO89*, plasma membrane Na+/Pi cotransporter] in response to high inhibition concentration of NP. Of these genes, *SUE1* and *PHO89* did not meet the first criterion. These genes were chosen due to their highly increased expression upon exposure to NP. *CCW12* that encodes a mannoprotein required for cell wall integrity during budding and the formation of mating projections (Ragni et al. 2011) and used as a reference gene in our previous study (Bereketoglu et al. 2016) was selected as an internal control. No changes in the mRNA expression of this gene were observed in our microarray data in response to NP exposure. As a result, the quantitative real-time RT-PCR data and microarray data were highly consistent with a Pearson correlation of 0.935 for the compared genes (Table 3.12). These observations verify that our microarray results reflect accurately the changes in gene expression in *S. cerevisiae* upon exposure to NP.

Table 3.12 Comparison of gene expression levels of nonylphenol (NP) using quantitative real-time RT-PCR and microarray data

Gene	**Description of gene product**	**Real-time RT-PCR**		**Microarray**	
		Fold change	**P value**	**Fold change**	**P value**
PDR5	Plasma membrane ATP-binding cassette (ABC) transporter	+5.6	1.61E-07	+2.0	9.56E-07
PDR16	Plasma membrane ATP-binding cassette (ABC) transporter	+2.0	2.94E-07	+2.2	2.00E-07
SNQ2	Plasma membrane ATP-binding cassette (ABC) transporter	+1.9	7.97E-04	+1.5	1.65E-04
PHO89	Plasma membrane Na+/Pi cotransporter	+5.0	7.99E-09	+2.4	3.91E-07

Table 3.12 continued

FRE1	Ferric reductase	+4.1	2.81E-09	+1.8	1.21E-05
CTR3	Copper transporter	+3.9	6.18E-09	+2.6	4.03E-07
SUE1	Nuclear protein	+7.1	4.62E-13	+3.3	1.03E-06
COX4	Cytochrome c oxidase	-1.9	5.26E-09	-1.8	5.04E-06
QCR2	Cytochrome c oxidoreductase	-2.0	8.75E-06	-1.8	1.73E-05
QCR7	ubiquinol-cytochrome c oxidoreductase	-1.6	1.84E-06	-1.8	3.16E-05

4. CONCLUSION

In the literature, to date, most of the studies have investigated the effects of EDCs, including BPA and NP, on specific genes or group of genes using real-time PCR or DNA microarray while there has been no study focused on the effects of such chemicals at the whole genome level. Within this context, the present study analyzed genome-wide transcriptional profiles of single-celled model organism-*S. cerevisae* upon exposure to low and high inhibition concentrations of BPA and NP. For BPA exposure, 50 mg/L BPA was used as low inhibition concentration while 300 mg/L BPA was chosen as high inhibition concentration. On the other hand, 1 and 5 mg/L NP were used as low and high inhibition concentrations for NP exposure, respectively. High inhibition concentrations of both BPA and NP resulted in severe effects on various processes and several genes, with substantial changes in expression, while low inhibition concentrations showed modest changes in expression of small number of genes. Although similar processes were affected by exposure to distinct BPA and NP concentrations, the number and magnitude of differentially expressed genes differ between low and high inhibition concentration treatments.

Exposure to low inhibition concentration of BPA triggers mechanisms associated with cell cycle progression and DNA repair, while high inhibition concentration of BPA cause defects in mitochondrial processes, particularly in energy metabolism. In addition, high inhibition concentration of BPA may reduce nutrient allocation to the appropriate compartments by preventing cells to uptake iron and copper. Moreover, yeast cells attempt to overcome BPA toxicity, particularly the decreased growth rate, by upregulating ribosomal biogenesis in response to high inhibition concentration of BPA. Besides, both low and high inhibition concentrations of BPA triggers the PDR network in yeast cells.

Yeast cells may adapt to low levels of NP in time, because the expression level of several affected genes returned to pre-stimulated levels after 180 min exposure. In addition, low inhibition concentration of NP exposure may result in induction of Atg genes to balance lack of essential amino acids for cell survival. On the other hand, high inhibition concentration of NP may damage the cell wall and yeast cells upregulate

many genes encoding cell wall proteins and functioning in cell wall biosynthesis to overcome this possible NP toxicity. Moreover, high levels of NP may cause cellular stress leading abnormal and/or nonfunctional proteins. In conclusion, the presented results provide insight into the subcellular effects of BPA and NP which showed that yeast cells respond to BPA and NP in a concentration-dependent manner via different genes.

In the future studies, it is planning to analyze the long-term effects of BPA and NP at much lower concentrations to simulate the realistic contamination scenarios considering continuous release and possible accumulation of BPA and NP in the environment. It is also planning to obtain possible gene targets (biomarkers) by combining and analyzing the present results with future data. Moreover, by focusing on specific cellular mechanisms, such as OXPHOS, MDR, cell cycle progression, ribosomal and cell wall biogenesis etc., it is aimed to investigate the effects of these chemicals on higher eukaryotes using cell lines.

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SUPPLEMENTARY MATERIALS

Table S1 Primers used for quantitative real-time reverse transcription (RT)-PCR-based validation of microarray data (F:Forward, R:Reverse)

Primer Name	ORF	Primer Sequence (5' → 3')	Amplicon Size (bp)	Reference
*NDI1*_F	YML120C	CCCGACAGGAATACCGTTACCA	137	This study
*NDI1*_R		TCCGCACCTACAGCACTGATTA		
*SDH1*_F	YKL148C	GGTGGTATCAATGCCGCTCTG	113	This study
*SDH1*_R		ATGTAATGGATGGAGTCCTGGTCA		
*QCR2*_F	YPR191W	GCAGGTAAGTCATTGGTGAGTAA	166	This study
*QCR2*_R		CGGATAGGGCAGAGGTCAAA		
*QCR7*_F	YDR529C	GTCCTCTCCAAGTTATGTGTTCCA	187	This study
*QCR7*_R		CGGTTTGATGAGCCCTGATTATTC		
*COX4*_F	YGL187C	AACCATTAGATTCGTCCAGGAAGG	109	This study
*COX4*_R		GTATGTGAACCAGCGGGAGAAC		
*ATP3*_F	YBR039W	TGACCCAGTGTCTTCCCTATCTTT	185	This study

Table S1 continued

*ATP3*_R		CAGCAGCATAACCTTGAGCCATT		
*PDR5*_F	YOR153W	TGACGCTTTTGCATCAGTTC	150	a
*PDR5*_R		GAGAAAACCGCGACAATGTT		
*PDR16*_F	YNL231C	AGGGCTACTAAATGGGTGCTAA	154	This study
*PDR16*_R		CCTGCTTACCTGATTCGTTCTC		
*SNQ2*_F	YDR011W	TATCAAAAGCTGGCCAATCC	103	a
*SNQ2*_R		GTTTGTCCACCCTTCCTCAA		
*UTP23*_F	YOR004W	GGTATGTGGTTGCTTCTCAGGAC	148	This study
*UTP23*_R		TGTTCTTCAGTAATCTTGCTTGCC		
*NOP15*_F	YNL110C	CCAAACAACCCACCGAAGAA	144	This study
*NOP15*_R		TACCGCTCTGCTCATCATCA		
*CIN2*_F	YPL241C	ATGTCTTGGAGAAGGGTGATTCAG	102	This study
*CIN2*_R		ACAAAGAACCAGAAAGGGCACTAT		
FRE1_F	YLR214W	GCGAACGAGACAGCGTATCATT	115	This study

Table S1 continued

FRE1_R		TAAGCACAGCCACCCAGAAGAA		
CTR3_F	YLR411W	ACGAGCCAGAAGACGACCT	210	This study
CTR3_R		AACGACCAACGATAGCACCTA		
SUE1_F	YPR151C	GTGGCACTGGTGGTATAATGTC	277	This study
SUE1_R		TGTCAAACGGCTTCAACTTTCT		
*PHO89*_F	YBR296C	GGTTCTGGCTTATGGTGGTGTTG	188	This study
*PHO89*_R		CGATCTGGGTTGTTGAGGTAGGA		
*CCW12*_F	YLR110C	TTTGGTTTCCACCGCTAC	149	b
*CCW12*_R		CAGCAGAGGTGGTGTTCTTT		

a) Ma, M., Liu, Z.L., (2010) Comparative transcriptome profiling analysis during the lag phase uncover YAP1, PDR1, PDR3, RPN4, and HSF1 as key regulatory genes in genomic adaptation to the lignocellulose derived inhibitor HMF for *Saccharomyces cerevisiae*. BMC Genomics, 11, 660.

b) Cankorur-Cetinkaya, A., Dereli, E., Eraslan, S., Karabekmez, E., Dikicioglu, D., et al., (2012) A novel strategy for selection and validation of reference genes in dynamic multidimensional experimental design in yeast. PLoS ONE, 7(6): e38351. doi: 10.1371/journal.pone.0038351.

Table S2 Complete list of differentially expressed genes in *S. cerevisiae* exposed to 50 mg/L bisphenol A (BPA)

Downregulated			Upregulated		
ORF	**Fold change**	**P-Value**	**ORF**	**Fold change**	**P-Value**
YPL095C	1.6	0.0001	YHL009W-A	1.6	0.0436
YMR011W	1.4	0.0185	YNL018C	1.6	0.0094
YOR032C	1.4	0.0044	YOR049C	1.5	0.0073
YMR035W	1.4	0.0354	YNL034W	1.5	0.0492
YIL029C	1.3	0.0223	YMR304W	1.4	0.0468
YPR192W	1.3	0.0051	YGR281W	1.4	0.0017
YEL069C	1.3	0.0014	YGR109W-B	1.4	0.0081
YLR414C	1.3	0.0197	YOR153W	1.4	0.0024
YMR230W-A	1.3	0.0125	YCR014C	1.4	0.0129
YPR001W	1.3	0.0104	YBR152W	1.4	0.0206
YIR021W-A	1.3	0.0014	YGL192W	1.4	0.0069
YMR316W	1.3	0.0465	YHR023W	1.4	0.0206
YNR075C-A	1.3	0.0330	YAL016C-B	1.3	0.0121
YOR068C	1.3	0.0418	YGR035C	1.3	0.0113
YNR061C	1.3	0.0494	YDR524W-A	1.3	0.0352
YGR247W	1.3	0.0242	YNR066C	1.3	0.0420
YPL250C	1.3	0.0224	YNL328C	1.3	0.0431
YHR214C-E	1.3	0.0181	YDL058W	1.3	0.0406
YMR040W	1.3	0.0443	YDR446W	1.3	0.0058
YER042W	1.3	0.0267	YMR207C	1.3	0.0220

Table S2 continued

YLR008C	1.3	0.0243	YIL082W-A	1.3	0.0166
YGL126W	1.3	0.0382	YJR035W	1.3	0.0214
YGR197C	1.3	0.0100	YPL167C	1.3	0.0068
YDR236C	1.2	0.0385	YOL101C	1.3	0.0049
YPL274W	1.2	0.0044	YDL070W	1.3	0.0419
YNR057C	1.2	0.0188	YIL112W	1.3	0.0306
YFR032C	1.2	0.0206	YIR033W	1.3	0.0172
YIL023C	1.2	0.0123	YDR314C	1.3	0.0102
YLR460C	1.2	0.0203	YFL051C	1.3	0.0491
YDR106W	1.2	0.0496	YAR068W	1.3	0.0181
YIL072W	1.2	0.0186	YPL158C	1.2	0.0324
YNR004W	1.2	0.0310	YBL049W	1.2	0.0158
YEL057C	1.2	0.0057	YNL188W	1.2	0.0361
YML022W	1.2	0.0381	YDL056W	1.2	0.0375
YBR005W	1.2	0.0386	YDR379W	1.2	0.0266
YPL149W	1.2	0.0411	YJL130C	1.2	0.0331
YER076C	1.2	0.0368	YCR042C	1.2	0.0450
YER073W	1.2	0.0226	YDR200C	1.2	0.0231
YLL056C	1.2	0.0346	YBR208C	1.2	0.0070
YNL220W	1.2	0.0350	YHR158C	1.2	0.0300
YOR376W-A	1.2	0.0371	YDR176W	1.2	0.0203
YHR128W	1.2	0.0285	YML054C-A	1.2	0.0202
YBL029C-A	1.2	0.0373	YDR085C	1.2	0.0135

Table S2 continued

YPL162C	1.2	0.0108	YIL011W	1.2	0.0406
YOR180C	1.2	0.0440	YKR029C	1.2	0.0461
YLR415C	1.2	0.0167	YMR219W	1.2	0.0427
YHR049W	1.2	0.0201	YKL050C	1.2	0.0446
YDL246C	1.2	0.0122	YOR304W	1.2	0.0372
YNL320W	1.2	0.0439	YGR186W	1.2	0.0274
YOL008W	1.2	0.0373	YGR059W	1.2	0.0340
YJR011C	1.2	0.0186	YHR007C-A	1.2	0.0117
YGL166W	1.2	0.0310	YGL133W	1.2	0.0301
YDR380W	1.2	0.0275	YOL166W-A	1.2	0.0319
YMR243C	1.2	0.0473	YGL151W	1.2	0.0186
YBL057C	1.2	0.0472	YDL239C	1.2	0.0273
YER185W	1.2	0.0216	YKL101W	1.2	0.0374
YLR377C	1.2	0.0473	YOL006C	1.2	0.0385
YNR059W	1.2	0.0226	YCL061C	1.2	0.0275
YMR157C	1.2	0.0447	YAR064W	1.2	0.0246
YOR213C	1.2	0.0378	YMR179W	1.2	0.0459
YGL256W	1.2	0.0344	YMR075W	1.2	0.0381
YGR087C	1.2	0.0383	YOR372C	1.2	0.0499
YBR135W	1.2	0.0482	YDR186C	1.2	0.0475
YKR052C	1.2	0.0382	YOR191W	1.2	0.0381
YCR098C	1.2	0.0400	YOL100W	1.2	0.0212
YPR128C	1.2	0.0403	YNL088W	1.2	0.0345

Table S2 continued

YGR031W	1.2	0.0384	YJL162C	1.2	0.0475
YDR489W	1.2	0.0400	YGL086W	1.2	0.0465
YGL257C	1.2	0.0389	YJR089W	1.2	0.0458
YCR105W	1.2	0.0336	YPR179C	1.2	0.0134
YJL065C	1.2	0.0454	YLR238W	1.2	0.0203
YGL263W	1.2	0.0215	YCL025C	1.2	0.0373
YER156C	1.2	0.0249	YGR009C	1.2	0.0505
YFL011W	1.2	0.0323	YNL118C	1.2	0.0322
YMR021C	1.2	0.0348	YNL225C	1.2	0.0277
YDL217C	1.2	0.0297	YPR174C	1.2	0.0451
YLR180W	1.2	0.0489	YEL061C	1.2	0.0306
YLR004C	1.1	0.0360	YHR080C	1.2	0.0421
YAL063C-A	1.1	0.0382	YIL026C	1.2	0.0223
YOR297C	1.1	0.0389	YGR238C	1.2	0.0492
YLL054C	1.1	0.0455	YCL024W	1.2	0.0276
			YNL231C	1.2	0.0136
			YMR172W	1.2	0.0495
			YDR218C	1.2	0.0432
			YNL272C	1.2	0.0434
			YML051W	1.2	0.0423
			YMR232W	1.2	0.0338
			YJL077W-B	1.2	0.0394
			YER159C	1.2	0.0262

Table S2 continued

			YPL110C	1.2	0.0312
			YOR124C	1.2	0.0482
			YGL163C	1.2	0.0423
			YPL075W	1.2	0.0501
			YJR061W	1.2	0.0431
			YDL028C	1.2	0.0414
			YPR138C	1.2	0.0324
			YAL064W	1.2	0.0428
			YPR121W	1.2	0.0498
			YCL064C	1.2	0.0313
			YPR171W	1.2	0.0444
			YDR289C	1.2	0.0416
			YHR053C	1.1	0.0470
			YOR293C-A	1.1	0.0388
			YLR099C	1.1	0.0468

Table S3 Complete list of differentially expressed genes in *S. cerevisiae* exposed to 300 mg/L bisphenol A (BPA)

Downregulated			Upregulated		
ORF	**Fold change**	**P-Value**	**ORF**	**Fold change**	**P-Value**
YPR160W	4.1	6.67E-05	YER106W	27.0	3.14E-06
YHL028W	3.9	6.06E-08	YGR059W	25.0	3.33E-07
YFR053C	3.6	3.06E-05	YMR101C	24.2	3.25E-09
YPR194C	3.6	2.56E-06	YPL130W	18.2	2.70E-08
YHR092C	3.3	1.32E-05	YLR412C-A	15.8	1.33E-06
YDR380W	3.2	7.22E-08	YPL021W	13.4	4.45E-08
YMR250W	3.1	1.68E-04	YDR522C	11.1	1.11E-06
YDR342C	3.1	6.12E-05	YGR142W	11.0	1.15E-06
YFR015C	3.1	1.09E-05	YPL250C	11.0	1.08E-06
YMR105C	3.0	1.90E-04	YDR523C	10.9	6.50E-08
YEL024W	2.8	3.34E-06	YBR296C	10.4	3.56E-06
YBR054W	2.8	8.14E-06	YKL107W	10.0	7.73E-06
YEL011W	2.8	2.53E-04	YDR256C	9.8	3.14E-05
YKL148C	2.7	4.68E-07	YGL032C	9.6	1.38E-06
YLL064C	2.7	8.10E-06	YMR013W-A	9.4	2.99E-07
YHL021C	2.6	6.81E-05	YLL046C	9.2	3.92E-06
YNR034W-A	2.6	6.52E-04	YFR032C	8.7	2.14E-07
YER067W	2.6	5.95E-04	YGR161C	8.6	5.64E-06
YKL103C	2.6	3.09E-05	YGR273C	8.5	7.87E-07
YGR248W	2.6	3.32E-03	YGR243W	8.2	8.60E-07

Table S3 continued

YPL095C	2.5	9.14E-07	YNL077W	8.1	9.92E-07
YCL040W	2.4	2.72E-04	YHR079C-A	7.9	8.33E-07
YDL021W	2.4	3.10E-04	YHR176W	7.9	6.79E-09
YBR183W	2.4	5.62E-05	YER104W	7.8	7.22E-05
YJL052W	2.3	2.52E-04	YLR307C-A	7.7	1.92E-06
YBR072W	2.3	6.34E-03	YGR035C	7.4	1.66E-08
YOR230W	2.3	9.86E-06	YJL047C-A	7.1	6.52E-09
YGL104C	2.3	2.87E-05	YLR411W	6.8	2.01E-08
YCL049C	2.3	2.47E-05	YGR236C	6.5	1.08E-05
YHR001W-A	2.3	4.73E-06	YIL057C	6.4	3.88E-06
YGR254W	2.3	5.12E-05	YPR151C	6.3	3.62E-05
YGR032W	2.3	4.57E-04	YBR072C-A	5.9	8.90E-05
YDR516C	2.2	1.53E-05	YBR298C-A	5.9	1.08E-06
YLR258W	2.2	6.21E-04	YOR154W	5.8	7.17E-07
YIL124W	2.2	4.83E-06	YPL027W	5.7	1.71E-07
YDL181W	2.2	3.53E-05	YDL020C	5.6	4.32E-06
YER053C	2.2	3.67E-04	YHR094C	5.6	1.42E-06
YML120C	2.2	5.08E-05	YGR213C	5.5	5.22E-06
YDL022W	2.2	1.44E-04	YLR081W	5.5	2.29E-07
YKL062W	2.2	2.75E-05	YPL171C	5.4	3.66E-04
YDR148C	2.2	4.23E-06	YOL156W	5.4	1.98E-04
YPL123C	2.2	4.65E-05	YJL219W	5.4	4.21E-04
YDR058C	2.2	2.21E-05	YGR212W	5.1	3.01E-07

Table S3 continued

YPL267W	2.2	6.03E-06	YNR066C	5.0	6.21E-07
YBR139W	2.2	1.69E-05	YHR177W	4.8	8.49E-08
YIL070C	2.1	3.97E-06	YBL043W	4.8	3.28E-04
YBL029W	2.1	4.24E-06	YPL033C	4.7	1.08E-05
YGL037C	2.1	7.01E-05	YPL060W	4.6	7.75E-08
YMR256C	2.1	1.41E-06	YBR066C	4.5	4.69E-05
YPR191W	2.1	3.14E-05	YOR351C	4.5	6.28E-07
YBR251W	2.1	2.22E-06	YDR218C	4.4	2.17E-05
YLR069C	2.1	1.06E-05	YDR403W	4.4	3.30E-05
YDL178W	2.1	7.81E-07	YOL151W	4.3	9.98E-05
YJR103W	2.1	8.83E-06	YDL037C	4.3	1.19E-05
YDR529C	2.1	3.68E-06	YKL183C-A	4.2	1.01E-07
YCL030C	2.1	9.08E-06	YHR139C	4.2	1.12E-06
YHR087W	2.0	1.08E-02	YOR178C	4.2	7.06E-03
YOL122C	2.0	4.30E-06	YPL201C	4.1	3.63E-08
YJR025C	2.0	1.24E-05	YNL075W	4.1	6.21E-06
YKL150W	2.0	1.47E-04	YLR214W	4.1	2.62E-06
YLR133W	2.0	3.52E-06	YMR251W	4.1	8.32E-05
YOR288C	2.0	1.84E-05	YGR052W	4.0	2.62E-03
YMR120C	2.0	9.56E-04	YPL241C	3.9	7.14E-06
YHL018W	2.0	6.78E-05	YEL065W	3.9	1.89E-06
YDL130W-A	2.0	1.54E-05	YGR249W	3.8	2.64E-04
YIL014C-A	2.0	1.82E-05	YLR341W	3.8	1.29E-04

Table S3 continued

YGR194C	2.0	2.84E-05	YLL028W	3.7	3.73E-07
YLL041C	2.0	2.61E-05	YJL030W	3.7	5.10E-07
YOR317W	2.0	2.47E-06	YFL040W	3.7	1.20E-06
YHR207C	2.0	4.92E-06	YLR346C	3.7	4.36E-05
YGR108W	2.0	2.46E-06	YIL056W	3.7	2.35E-05
YER187W	2.0	6.03E-06	YDR246W-A	3.7	2.02E-06
YBR241C	2.0	6.98E-05	YDL038C	3.6	7.53E-05
YNL289W	2.0	4.95E-05	YBR056W-A	3.6	2.46E-03
YMR222C	2.0	5.75E-06	YJR095W	3.6	6.97E-04
YLR178C	2.0	2.69E-03	YNL277W-A	3.5	6.62E-06
YHR049W	2.0	1.93E-06	YKR097W	3.4	1.00E-07
YLR270W	2.0	5.24E-05	YJL033W	3.4	5.76E-06
YLR301W	2.0	1.56E-06	YOL014W	3.4	2.35E-06
YHR137W	1.9	1.43E-06	YBL008W-A	3.4	1.33E-07
YIL111W	1.9	9.09E-05	YDR070C	3.4	4.85E-05
YGR080W	1.9	1.36E-05	YIR018C-A	3.4	5.79E-05
YOR099W	1.9	2.40E-06	YAL037C-A	3.4	1.57E-07
YGL191W	1.9	2.30E-04	YLR108C	3.4	2.18E-07
YMR152W	1.9	3.79E-06	YMR317W	3.4	3.15E-07
YCR075C	1.9	2.74E-06	YOR134W	3.3	3.40E-04
YBR039W	1.9	1.64E-05	YPR159C-A	3.3	5.50E-06
YOR032C	1.9	1.37E-03	YOL155W-A	3.3	1.03E-03
YOR128C	1.9	2.30E-05	YDR384C	3.3	1.21E-07

Table S3 continued

YJL186W	1.9	3.51E-05	YDL039C	3.3	1.29E-04
YDR518W	1.9	2.58E-06	YAL037W	3.2	5.07E-06
YMR110C	1.9	3.02E-05	YOR072W-B	3.2	1.95E-07
YKL035W	1.9	3.44E-05	YEL070W	3.2	6.35E-08
YKL178C	1.9	2.12E-06	YNR069C	3.2	7.15E-05
YEL039C	1.9	2.14E-03	YLR142W	3.2	1.48E-05
YHR008C	1.9	1.40E-05	YOR384W	3.1	1.42E-04
YOL030W	1.9	1.08E-05	YOR237W	3.1	9.31E-07
YJL161W	1.9	1.03E-03	YNR060W	3.1	8.14E-07
YOL094C	1.9	1.09E-04	YGR239C	3.0	1.41E-05
YBR214W	1.9	8.69E-04	YDR253C	3.0	7.67E-05
YDR100W	1.9	7.58E-06	YIL134C-A	3.0	5.11E-05
YMR210W	1.9	2.74E-06	YKL106C-A	3.0	8.63E-07
YJL180C	1.9	3.46E-06	YCR010C	3.0	3.20E-06
YDL110C	1.9	5.57E-04	YMR107W	3.0	3.76E-04
YBL045C	1.9	1.58E-06	YOR382W	3.0	4.75E-04
YBR037C	1.9	1.05E-04	YDR042C	3.0	3.67E-06
YGL038C	1.9	2.04E-05	YGR146C	3.0	4.83E-07
YGR008C	1.9	4.67E-04	YEL048C	2.9	7.62E-07
YDR539W	1.9	1.88E-06	YGR146C-A	2.9	1.05E-07
YGR165W	1.9	1.01E-05	YOL149W	2.9	6.00E-04
YPL113C	1.9	7.80E-04	YPR108W-A	2.9	2.47E-06
YBR185C	1.9	5.75E-05	YOR348C	2.9	4.56E-04

Table S3 continued

YER062C	1.9	1.28E-05	YNL095C	2.9	2.57E-05
YDR322W	1.8	7.12E-06	YNR068C	2.9	3.28E-05
YBL091C-A	1.8	1.62E-05	YKL070W	2.8	2.58E-04
YML100W	1.8	4.13E-03	YHR096C	2.8	2.19E-04
YAL016C-B	1.8	1.05E-02	YPR040W	2.8	1.93E-07
YBR046C	1.8	1.84E-05	YLR136C	2.8	8.42E-07
YNL322C	1.8	3.95E-05	YNL008C	2.8	1.16E-04
YBR056W	1.8	2.03E-04	YFR032C-B	2.8	1.20E-04
YLR244C	1.8	1.83E-05	YOR192C-C	2.7	4.38E-06
YNL052W	1.8	6.38E-05	YER028C	2.7	6.63E-07
YER080W	1.8	1.02E-05	YNL145W	2.7	5.17E-06
YGL065C	1.8	3.40E-05	YBR119W	2.7	2.61E-07
YKL194C	1.8	2.73E-05	YIL019W	2.7	7.35E-06
YOR176W	1.8	9.96E-06	YGR211W	2.7	8.24E-07
YKL193C	1.8	1.94E-05	YJL144W	2.7	1.10E-03
YKR066C	1.8	1.37E-05	YAR071W	2.7	6.58E-06
YGL187C	1.8	7.90E-05	YLR406C-A	2.6	3.31E-05
YHR113W	1.8	1.35E-05	YOR338W	2.6	7.29E-04
YBR041W	1.8	5.29E-06	YHR214C-D	2.6	4.02E-06
YKR067W	1.8	6.77E-06	YCL026C-A	2.6	2.12E-04
YNL220W	1.8	7.25E-05	YHL040C	2.6	2.28E-04
YGL087C	1.8	9.23E-06	YOR293C-A	2.6	1.89E-05
YPL215W	1.8	3.32E-06	YJL170C	2.6	2.52E-05

Table S3 continued

YPR098C	1.8	1.06E-04	YJR005C-A	2.6	2.45E-03
YOR215C	1.8	1.17E-04	YBR065C	2.6	5.02E-05
YCR003W	1.8	1.12E-05	YIL172C	2.6	1.52E-03
YER027C	1.8	5.70E-06	YDR281C	2.6	1.49E-04
YGR295C	1.8	3.33E-05	YJL153C	2.6	2.23E-05
YJL079C	1.8	1.84E-03	YOL158C	2.6	8.73E-07
YJL091C	1.8	5.95E-06	YOR214C	2.6	9.83E-06
YOR313C	1.8	6.64E-06	YPR015C	2.5	3.99E-06
YJR079W	1.8	1.83E-04	YOR268C	2.5	4.55E-05
YLR162W-A	1.8	7.60E-06	YPR124W	2.5	1.02E-05
YJL181W	1.8	2.09E-05	YBL054W	2.5	6.29E-04
YFR008W	1.8	4.83E-05	YOR298W	2.5	8.91E-06
YOL082W	1.8	7.92E-05	YMR017W	2.5	1.27E-02
YKL091C	1.8	1.31E-04	YDR223W	2.5	1.09E-04
YJL102W	1.8	3.55E-05	YHR054C	2.5	1.69E-04
YHR140W	1.8	1.97E-03	YOR328W	2.5	1.02E-05
YDR277C	1.8	2.27E-04	YER103W	2.5	3.78E-03
YLR121C	1.8	5.18E-05	YHL047C	2.5	4.69E-04
YOL033W	1.8	1.92E-05	YOR302W	2.5	1.63E-06
YER141W	1.8	2.91E-06	YLR213C	2.5	3.20E-06
YLR356W	1.8	1.04E-04	YOR383C	2.4	9.81E-04
YDL086W	1.8	2.94E-05	YMR133W	2.4	8.31E-05
YGR138C	1.7	2.69E-04	YOL013W-B	2.4	8.15E-04

Table S3 continued

YLR359W	1.7	5.24E-05	YEL076C	2.4	2.50E-04
YJL053W	1.7	3.11E-05	YGL209W	2.4	3.20E-04
YDR284C	1.7	7.53E-06	YJL088W	2.4	1.14E-06
YHR059W	1.7	1.59E-05	YPL088W	2.4	2.52E-07
YNL274C	1.7	1.03E-03	YCR047C	2.4	4.26E-06
YDR475C	1.7	2.83E-05	YER185W	2.4	3.29E-04
YML091C	1.7	7.48E-05	YLR323C	2.4	5.70E-07
YAR028W	1.7	9.72E-05	YDL182W	2.3	2.36E-06
YMR092C	1.7	4.10E-05	YHL009W-A	2.3	6.03E-03
YNR001C	1.7	1.35E-05	YIL046W-A	2.3	4.74E-06
YIL076W	1.7	5.13E-06	YOR152C	2.3	2.73E-03
YJL068C	1.7	4.88E-06	YIL127C	2.3	1.25E-05
YJL171C	1.7	5.38E-05	YHR214C-E	2.3	1.68E-04
YDL237W	1.7	7.67E-06	YDR171W	2.3	6.51E-03
YBL098W	1.7	1.55E-05	YGL006W-A	2.3	1.91E-05
YLR201C	1.7	9.76E-05	YOR204W	2.3	5.85E-07
YOR125C	1.7	7.62E-05	YLR281C	2.3	7.79E-06
YLR354C	1.7	5.73E-06	YPL058C	2.3	1.45E-03
YDR055W	1.7	1.09E-04	YGL029W	2.3	1.34E-04
YBR088C	1.7	1.17E-04	YPR158W	2.3	3.89E-04
YNR044W	1.7	1.02E-04	YJR097W	2.3	4.11E-04
YOR187W	1.7	7.52E-06	YLR156W	2.3	5.28E-05
YHL002W	1.7	4.53E-06	YAR064W	2.3	9.57E-06

Table S3 continued

YKL189W	1.7	3.94E-05	YMR230W-A	2.3	2.00E-05
YLR203C	1.7	1.04E-04	YMR011W	2.3	1.87E-04
YHR051W	1.7	2.19E-05	YCL048W	2.3	1.98E-04
YCR073W-A	1.7	3.17E-05	YOR339C	2.3	7.87E-07
YOL114C	1.7	2.50E-04	YER179W	2.3	1.75E-05
YBR126C	1.7	1.59E-03	YMR016C	2.3	3.75E-05
YMR251W-A	1.7	1.14E-04	YLR073C	2.3	1.12E-04
YOR155C	1.7	3.02E-04	YBR301W	2.2	7.58E-06
YKR016W	1.7	3.18E-05	YLL027W	2.2	2.97E-05
YLR306W	1.7	1.88E-05	YOR303W	2.2	1.13E-05
YNL160W	1.7	3.70E-03	YNL146C-A	2.2	1.70E-04
YBR053C	1.7	6.27E-05	YBR018C	2.2	3.34E-04
YDL103C	1.7	1.93E-05	YNL067W-B	2.2	1.46E-03
YGR004W	1.7	1.40E-05	YDR034W-B	2.2	1.03E-04
YML126C	1.7	1.71E-05	YJL089W	2.2	1.19E-03
YLR423C	1.7	1.14E-04	YPR116W	2.2	1.12E-06
YDR368W	1.7	2.36E-05	YIL015W	2.2	3.67E-04
YDR204W	1.7	8.04E-05	YBR219C	2.2	2.12E-05
YLL007C	1.7	1.79E-04	YJR115W	2.2	1.34E-05
YBL064C	1.7	3.67E-04	YDL129W	2.2	1.42E-05
YJR019C	1.7	8.38E-05	YNL149C	2.2	9.75E-07
YNL223W	1.7	1.28E-04	YGR159C	2.2	6.03E-05
YKL142W	1.7	5.44E-04	YHR175W	2.2	8.25E-07

Table S3 continued

YAR027W	1.7	1.28E-04	YOR365C	2.2	3.56E-05
YHR202W	1.7	6.27E-05	YMR084W	2.2	3.39E-05
YDR032C	1.7	3.65E-05	YLR312C	2.2	2.10E-04
YDL091C	1.7	2.20E-05	YMR102C	2.2	6.78E-06
YMR297W	1.7	3.83E-04	YAL059W	2.2	3.65E-06
YMR173W	1.7	2.35E-04	YMR118C	2.2	1.41E-04
YBR169C	1.7	1.38E-03	YPL239W	2.1	1.82E-06
YDR191W	1.7	9.68E-05	YBR104W	2.1	1.13E-04
YDR175C	1.7	8.73E-06	YNL076W	2.1	1.48E-04
YMR228W	1.7	2.48E-05	YOR394W	2.1	2.91E-03
YNL315C	1.7	1.31E-05	YLR267W	2.1	3.72E-04
YNR007C	1.7	2.21E-05	YNL251C	2.1	1.84E-06
YOR280C	1.6	1.77E-05	YML116W	2.1	4.69E-06
YKL141W	1.6	1.31E-04	YKL071W	2.1	3.87E-03
YNL305C	1.6	2.60E-05	YEL069C	2.1	6.02E-04
YMR193W	1.6	1.65E-04	YDR065W	2.1	4.57E-05
YBR230W-A	1.6	2.41E-04	YKL163W	2.1	6.98E-04
YDR092W	1.6	9.40E-06	YGL205W	2.1	9.94E-04
YNR041C	1.6	1.26E-04	YHR126C	2.1	1.02E-03
YIL093C	1.6	2.60E-05	YOL091W	2.1	1.29E-04
YGR021W	1.6	7.52E-05	YLR068W	2.1	4.53E-05
YKL085W	1.6	1.38E-04	YLR054C	2.0	3.86E-05
YMR281W	1.6	2.77E-05	YPL242C	2.0	4.64E-04

Table S3 continued

YDR379C-A	1.6	2.50E-04	YIL008W	2.0	2.90E-05
YDR304C	1.6	1.29E-05	YOR305W	2.0	8.71E-06
YCL055W	1.6	6.55E-05	YMR058W	2.0	8.02E-07
YOR081C	1.6	5.30E-05	YLR285C-A	2.0	2.70E-06
YPL163C	1.6	3.76E-05	YMR175W	2.0	8.77E-05
YHL048W	1.6	1.56E-05	YHR175W-A	2.0	8.97E-06
YFL052W	1.6	2.64E-03	YER078W-A	2.0	8.66E-05
YMR278W	1.6	3.12E-05	YOR381W-A	2.0	1.54E-04
YBR149W	1.6	3.00E-04	YGR240C-A	2.0	1.66E-05
YOL107W	1.6	1.35E-04	YML108W	2.0	2.75E-04
YFR027W	1.6	1.48E-04	YKL078W	2.0	8.49E-04
YEL012W	1.6	6.30E-05	YAR068W	2.0	4.14E-06
YOR291W	1.6	1.71E-04	YBR200W-A	2.0	7.17E-05
YDR307W	1.6	1.25E-05	YPL257W	2.0	2.10E-05
YNL219C	1.6	1.02E-05	YBR267W	2.0	1.80E-04
YKL034W	1.6	4.67E-05	YKL143W	2.0	1.11E-05
YDR506C	1.6	9.26E-05	YER044C-A	2.0	6.39E-05
YJL166W	1.6	5.00E-05	YOR145C	2.0	6.07E-05
YGR171C	1.6	2.25E-05	YMR069W	2.0	4.69E-06
YML092C	1.6	7.61E-05	YBR294W	2.0	2.71E-04
YGR049W	1.6	2.01E-04	YHL016C	2.0	2.68E-06
YOL031C	1.6	8.67E-06	YBR076W	2.0	9.13E-04
YGR288W	1.6	9.89E-05	YEL061C	2.0	1.41E-03

Table S3 continued

YGR225W	1.6	9.75E-04	YGL015C	2.0	5.21E-04
YDR089W	1.6	2.29E-05	YNL110C	2.0	2.80E-05
YGL001C	1.6	1.12E-05	YJL108C	2.0	1.10E-05
YMR099C	1.6	4.22E-05	YDR275W	2.0	2.23E-05
YJR048W	1.6	4.95E-05	YOR262W	2.0	3.36E-06
YNL144C	1.6	4.67E-04	YGL184C	2.0	6.38E-04
YJR047C	1.6	5.42E-05	YOR107W	2.0	9.52E-04
YDR305C	1.6	3.65E-05	YDR151C	2.0	5.14E-05
YOR156C	1.6	5.23E-03	YNL231C	2.0	5.43E-06
YHL017W	1.6	2.05E-05	YPL012W	1.9	2.22E-05
YNL252C	1.6	6.47E-05	YHR213W-A	1.9	1.63E-06
YNL058C	1.6	3.10E-05	YDL153C	1.9	5.12E-05
YGR117C	1.6	9.08E-06	YDR524C	1.9	5.98E-06
YFL062W	1.6	5.26E-05	YDR213W	1.9	6.09E-06
YMR272C	1.6	2.80E-05	YML054C	1.9	6.16E-04
YLR148W	1.6	3.14E-04	YOR183W	1.9	1.02E-04
YHR034C	1.6	2.14E-04	YPR193C	1.9	8.75E-07
YLR395C	1.6	8.66E-05	YHR040W	1.9	2.11E-04
YJR015W	1.6	2.41E-05	YOR049C	1.9	8.65E-03
YBR052C	1.6	2.41E-04	YAL025C	1.9	3.91E-04
YMR199W	1.6	1.03E-05	YJR120W	1.9	2.67E-04
YKL016C	1.6	3.08E-05	YML080W	1.9	8.38E-05
YML128C	1.6	2.08E-02	YMR030W-A	1.9	8.40E-05

Table S3 continued

YDL004W	1.6	1.02E-04	YPR157W	1.9	5.82E-04
YCR065W	1.6	2.17E-04	YJL136W-A	1.9	1.02E-04
YJR121W	1.6	4.27E-05	YAL067W-A	1.9	4.46E-04
YML021C	1.6	3.93E-04	YHR086W-A	1.9	1.47E-03
YBR026C	1.6	8.84E-04	YDR216W	1.9	5.15E-04
YKL157W	1.6	2.99E-04	YKL084W	1.9	3.61E-06
YPL031C	1.6	4.92E-05	YDR011W	1.9	8.44E-05
YBL016W	1.6	1.93E-05	YIL064W	1.9	2.22E-05
YPL236C	1.6	2.50E-04	YDL063C	1.9	1.14E-03
YJL132W	1.6	5.99E-04	YOR095C	1.9	2.24E-05
YAR007C	1.6	9.73E-05	YBL071W-A	1.9	4.12E-05
YIL157C	1.6	2.33E-04	YJL217W	1.9	2.36E-06
YJR118C	1.6	3.71E-05	YGR121W-A	1.9	2.75E-05
YIR036C	1.6	2.36E-04	YNL112W	1.9	3.68E-04
YPL007C	1.6	7.97E-05	YOR294W	1.9	1.10E-04
YNR018W	1.6	4.22E-05	YNL036W	1.9	9.06E-06
YFR044C	1.6	1.14E-05	YLR329W	1.9	1.09E-04
YCR086W	1.6	7.25E-04	YDR299W	1.9	3.56E-04
YCR091W	1.6	1.24E-03	YOL154W	1.9	2.74E-06
YPL096W	1.6	1.39E-04	YIL099W	1.9	8.56E-04
YHR016C	1.6	2.70E-03	YHL009W-B	1.9	4.50E-03
YLR312W-A	1.6	3.78E-05	YHR081W	1.9	2.07E-05
YGL141W	1.6	6.25E-05	YOL084W	1.9	1.16E-02

Table S3 continued

YDR116C	1.6	4.44E-05	YOR316C-A	1.8	7.54E-04
YMR024W	1.6	1.18E-05	YBL074C	1.8	1.27E-03
YHR104W	1.6	1.70E-03	YNL002C	1.8	2.01E-04
YIL097W	1.6	6.22E-05	YOL059W	1.8	8.46E-06
YIL125W	1.6	3.02E-04	YOR344C	1.8	1.37E-05
YPR081C	1.6	6.17E-05	YLL008W	1.8	2.63E-05
YHR076W	1.6	1.32E-05	YLR297W	1.8	1.37E-03
YBR003W	1.6	5.54E-05	YMR315W-A	1.8	1.28E-05
YKR006C	1.6	1.29E-04	YKR060W	1.8	1.18E-04
YGR255C	1.6	1.07E-05	YPL043W	1.8	1.73E-04
YGL040C	1.6	6.14E-05	YAL061W	1.8	2.35E-02
YPL004C	1.6	3.00E-04	YLL042C	1.8	3.29E-04
YFR045W	1.6	1.21E-04	YOR004W	1.8	2.35E-04
YOR065W	1.6	8.36E-04	YLL006W-A	1.8	5.73E-06
YPL189C-A	1.6	2.49E-03	YIL020C	1.8	1.99E-05
YML081C-A	1.6	4.23E-05	YDR361C	1.8	7.30E-06
YIR007W	1.6	9.69E-05	YOR381W	1.8	2.35E-04
YJL126W	1.6	1.49E-05	YJL122W	1.8	9.58E-05
YFL048C	1.6	8.15E-05	YGR245C	1.8	3.31E-05
YPL087W	1.5	1.27E-03	YFR057W	1.8	9.71E-04
YJR033C	1.5	2.72E-05	YCR087C-A	1.8	4.50E-05
YDR298C	1.5	2.90E-05	YNR064C	1.8	1.13E-03
YDR178W	1.5	1.13E-04	YDR441C	1.8	6.06E-06

Table S3 continued

YGR112W	1.5	1.49E-04	YCL036W	1.8	1.01E-03
YJL167W	1.5	1.77E-05	YDR014W	1.8	6.55E-05
YOR074C	1.5	1.17E-05	YCR083W	1.8	6.03E-06
YER033C	1.5	1.37E-04	YOR297C	1.8	1.54E-06
YMR072W	1.5	2.23E-05	YJR147W	1.8	2.14E-05
YJR004C	1.5	1.95E-04	YCL001W-A	1.8	3.22E-04
YNL115C	1.5	4.69E-04	YKR041W	1.8	1.30E-04
YLR143W	1.5	6.77E-04	YJL206C	1.8	2.12E-06
YJR083C	1.5	1.13E-04	YBL028C	1.8	4.17E-05
YBR302C	1.5	4.34E-05	YFL016C	1.8	2.75E-05
YGR253C	1.5	1.67E-04	YFR055W	1.8	8.78E-05
YBR040W	1.5	9.09E-04	YGL096W	1.8	5.03E-04
YMR060C	1.5	1.89E-04	YDR270W	1.8	3.69E-05
YNL117W	1.5	1.00E-04	YDR259C	1.8	7.50E-05
YMR025W	1.5	1.13E-03	YLR284C	1.8	7.18E-06
YNL168C	1.5	3.42E-05	YER006W	1.8	6.91E-05
YDR503C	1.5	1.13E-04	YNL277W	1.8	3.92E-04
YLR274W	1.5	4.23E-05	YIR017C	1.8	5.91E-03
YHR097C	1.5	1.01E-03	YLL034C	1.8	2.83E-05
YDL248W	1.5	5.47E-05	YDR111C	1.8	6.81E-06
YLR183C	1.5	2.64E-04	YGL220W	1.8	2.94E-06
YFR047C	1.5	3.03E-04	YGR103W	1.8	4.16E-04
YBR087W	1.5	5.80E-05	YLR009W	1.8	1.24E-04

Table S3 continued

YER044C	1.5	6.12E-05	YKL221W	1.8	5.30E-04
YGL047W	1.5	1.36E-04	YPL111W	1.8	1.15E-04
YOL126C	1.5	3.17E-04	YDR406W	1.8	5.22E-03
YFR028C	1.5	3.17E-04	YLR012C	1.8	8.66E-04
YDL015C	1.5	2.12E-05	YDR365C	1.7	7.44E-04
YGL198W	1.5	5.94E-05	YOR019W	1.7	7.74E-05
YLR438W	1.5	3.37E-04	YGR158C	1.7	1.14E-04
YJR119C	1.5	5.00E-04	YHR124W	1.7	2.37E-05
YKR093W	1.5	1.10E-04	YEL076C-A	1.7	7.94E-03
YIL154C	1.5	1.35E-04	YHL035C	1.7	5.10E-05
YAL017W	1.5	6.14E-05	YNL195C	1.7	2.90E-05
YGR028W	1.5	2.51E-04	YEL044W	1.7	3.98E-06
YCL035C	1.5	5.16E-04	YGL033W	1.7	7.73E-04
YDL067C	1.5	1.86E-04	YNL227C	1.7	3.29E-05
YER182W	1.5	2.16E-03	YCL021W-A	1.7	5.20E-06
YKL007W	1.5	9.31E-05	YDR087C	1.7	9.90E-05
YHR018C	1.5	1.03E-04	YJL133C-A	1.7	1.66E-04
YGL263W	1.5	2.06E-03	YMR014W	1.7	8.83E-05
YNL265C	1.5	1.42E-04	YOR056C	1.7	2.05E-04
YNL026W	1.5	2.31E-04	YLR221C	1.7	2.13E-05
YIR042C	1.5	1.09E-04	YDL031W	1.7	2.66E-05
YJR078W	1.5	9.30E-03	YLR287C	1.7	9.49E-05
YMR160W	1.5	6.66E-05	YNL308C	1.7	1.72E-04

Table S3 continued

YDL127W	1.5	1.35E-04	YER085C	1.7	2.09E-05
YBR010W	1.5	9.16E-05	YGL071W	1.7	4.49E-05
YPR139C	1.5	4.62E-04	YOR388C	1.7	2.27E-04
YBR157C	1.5	1.26E-03	YLR460C	1.7	8.79E-04
YGR205W	1.5	1.17E-03	YNR032C-A	1.7	1.07E-05
YIR008C	1.5	5.71E-05	YJL107C	1.7	1.69E-04
YBR184W	1.5	7.45E-04	YIL079C	1.7	9.54E-05
YIR039C	1.5	9.68E-03	YPR187W	1.7	3.34E-06
YBR014C	1.5	2.16E-04	YGL170C	1.7	2.86E-04
YIR037W	1.5	1.49E-04	YPL146C	1.7	1.13E-03
YJL026W	1.5	1.47E-04	YMR185W	1.7	1.14E-04
YCL028W	1.5	8.49E-05	YLR250W	1.7	3.11E-05
YFR007W	1.5	6.73E-05	YAR035W	1.7	2.47E-05
			YAR009C	1.7	1.32E-02
			YAL064W	1.7	1.76E-04
			YCL054W	1.7	2.75E-04
			YMR322C	1.7	3.93E-03
			YJL148W	1.7	1.99E-04
			YKL037W	1.7	3.11E-04
			YGR110W	1.7	2.18E-03
			YLR157W-C	1.7	4.58E-04
			YHR071W	1.7	1.34E-05
			YEL075C	1.7	7.12E-04

Table S3 continued

			YHR066W	1.7	3.81E-03
			YML113W	1.7	1.81E-04
			YDR366C	1.7	2.48E-04
			YOR308C	1.7	5.98E-04
			YHL022C	1.7	6.39E-05
			YLR342W-A	1.7	1.40E-04
			YGR063C	1.7	4.86E-06
			YGL045W	1.7	5.72E-03
			YFR001W	1.7	3.39E-05
			YPL068C	1.7	1.52E-04
			YKR092C	1.7	1.29E-05
			YOR119C	1.7	6.35E-04
			YGL111W	1.7	1.87E-04
			YHR105W	1.7	2.73E-04
			YKR025W	1.7	6.28E-05
			YHR197W	1.7	2.38E-04
			YMR294W	1.7	4.61E-05
			YCR020C	1.7	4.12E-04
			YDR182W-A	1.7	3.61E-04
			YLL051C	1.7	1.26E-05
			YOR047C	1.7	1.38E-04
			YKL055C	1.7	4.27E-05
			YPR036W-A	1.7	2.10E-05

Table S3 continued

			YLR385C	1.7	1.91E-02
			YGR121C	1.7	3.85E-04
			YKR081C	1.7	2.00E-04
			YOL097W-A	1.7	1.93E-05
			YMR239C	1.7	1.39E-03
			YCR051W	1.7	9.49E-06
			YLL052C	1.7	1.47E-05
			YMR009W	1.7	4.01E-04
			YCR018C	1.7	3.02E-05
			YOL155C	1.7	1.16E-03
			YJL035C	1.7	1.38E-05
			YKL172W	1.7	1.79E-04
			YPR002W	1.7	3.30E-04
			YMR175W-A	1.7	5.86E-04
			YGL086W	1.7	4.88E-05
			YGR145W	1.7	3.97E-04
			YLR196W	1.7	3.51E-04
			YDR222W	1.7	2.86E-04
			YAR066W	1.7	2.09E-04
			YIL002W-A	1.7	1.75E-05
			YBR090C	1.7	6.13E-05
			YPL252C	1.7	6.44E-06
			YGL183C	1.7	3.50E-04

Table S3 continued

			YNL009W	1.7	3.79E-03
			YKL099C	1.7	3.00E-04
			YDL241W	1.6	3.56E-04
			YGR016W	1.6	5.14E-04
			YHL015W-A	1.6	6.29E-03
			YCL059C	1.6	4.69E-05
			YLR099W-A	1.6	9.48E-06
			YGL179C	1.6	6.13E-05
			YER073W	1.6	9.51E-05
			YBR142W	1.6	3.67E-04
			YMR138W	1.6	9.20E-06
			YPL266W	1.6	1.43E-04
			YDL189W	1.6	1.24E-05
			YBL004W	1.6	1.32E-04
			YOR272W	1.6	6.08E-04
			YLR186W	1.6	5.18E-05
			YCR104W	1.6	1.35E-03
			YFL065C	1.6	1.04E-03
			YKL220C	1.6	2.36E-04
			YOR149C	1.6	1.40E-03
			YDL114W	1.6	1.45E-04
			YJL184W	1.6	9.92E-06
			YGL138C	1.6	9.84E-04

Table S3 continued

			YML018C	1.6	5.95E-04
			YLR328W	1.6	7.34E-06
			YDR374C	1.6	4.96E-03
			YOL101C	1.6	2.94E-04
			YPL069C	1.6	5.76E-05
			YGL243W	1.6	1.25E-05
			YJL098W	1.6	7.48E-04
			YOL010W	1.6	2.99E-03
			YML083C	1.6	9.50E-04
			YDR255C	1.6	1.08E-02
			YDR364C	1.6	2.57E-05
			YLR412W	1.6	3.35E-05
			YDR261C-D	1.6	2.74E-02
			YOL152W	1.6	1.19E-03
			YBR063C	1.6	2.02E-04
			YDR043C	1.6	3.34E-02
			YLR106C	1.6	7.62E-05
			YOL124C	1.6	1.64E-03
			YOR255W	1.6	3.41E-03
			YDR176W	1.6	1.12E-04
			YGR144W	1.6	7.52E-04
			YGL007C-A	1.6	8.91E-05
			YDR075W	1.6	6.03E-05

Table S3 continued

			YML118W	1.6	8.29E-05
			YIR018W	1.6	5.99E-05
			YPR066W	1.6	1.97E-04
			YLR415C	1.6	1.16E-03
			YOR190W	1.6	5.91E-05
			YLR462W	1.6	1.74E-03
			YDR397C	1.6	2.41E-05
			YDL223C	1.6	1.42E-04
			YPR119W	1.6	2.20E-05
			YDR398W	1.6	2.80E-03
			YOR306C	1.6	1.86E-04
			YNL187W	1.6	3.12E-04
			YCL012C	1.6	9.82E-05
			YDL213C	1.6	1.91E-04
			YIL055C	1.6	4.22E-04
			YIL096C	1.6	1.12E-03
			YLR154C-H	1.6	7.07E-03
			YHR185C	1.6	2.65E-02
			YNL113W	1.6	8.18E-05
			YOR363C	1.6	2.65E-05
			YJR108W	1.6	3.26E-03
			YHR089C	1.6	2.15E-05
			YHR157W	1.6	6.54E-05

Table S3 continued

			YEL072W	1.6	9.91E-05
			YNR012W	1.6	5.82E-04
			YDR227W	1.6	3.19E-05
			YLR099C	1.6	1.08E-03
			YOL104C	1.6	7.67E-05
			YIL102C	1.6	3.57E-03
			YJL078C	1.6	4.13E-04
			YPL211W	1.6	2.26E-04
			YNL299W	1.6	3.65E-04
			YGL098W	1.6	2.65E-05
			YOR153W	1.6	3.70E-04
			YGL014W	1.6	1.23E-04
			YBL049W	1.6	1.05E-02
			YNL014W	1.6	1.92E-04
			YOR377W	1.6	3.05E-05
			YPL126W	1.6	6.06E-04
			YPL230W	1.6	1.82E-02
			YMR095C	1.6	1.69E-02
			YIL160C	1.6	5.89E-03
			YLR200W	1.6	1.21E-05
			YHR033W	1.6	1.25E-04
			YOL136C	1.6	4.21E-04
			YHR048W	1.6	9.36E-03

Table S3 continued

			YOR371C	1.6	6.25E-05
			YOR159C	1.6	1.48E-04
			YDR402C	1.6	2.73E-03
			YKL108W	1.6	1.47E-03
			YOR192C	1.6	3.16E-05
			YIR026C	1.6	3.46E-04
			YDR346C	1.6	1.48E-04
			YLR074C	1.6	1.19E-03
			YMR290C	1.6	4.05E-04
			YKR075C	1.5	4.03E-03
			YOR385W	1.5	4.80E-04
			YGL158W	1.5	1.96E-03
			YDR016C	1.5	1.09E-04
			YGR079W	1.5	6.91E-03
			YGL041C-B	1.5	7.77E-04
			YHR044C	1.5	4.53E-04
			YNL132W	1.5	1.48E-04
			YOR283W	1.5	1.58E-05
			YNL254C	1.5	4.92E-04
			YGR210C	1.5	2.27E-05
			YER048W-A	1.5	3.54E-05
			YKL106W	1.5	1.57E-04
			YCR102C	1.5	6.05E-03

Table S3 continued

			YDL058W	1.5	9.86E-05
			YHR204W	1.5	1.45E-04
			YPR112C	1.5	2.76E-03
			YLL011W	1.5	3.19E-03
			YKL187C	1.5	1.69E-05
			YBL071C-B	1.5	5.40E-04
			YMR269W	1.5	3.21E-03
			YOL080C	1.5	5.64E-04
			YBL075C	1.5	4.77E-05
			YDL184C	1.5	4.47E-04
			YHR136C	1.5	5.82E-05
			YKL082C	1.5	7.76E-04
			YER137C	1.5	6.30E-04
			YFL056C	1.5	1.12E-03
			YDL167C	1.5	1.77E-03
			YJL191W	1.5	2.52E-04
			YNL175C	1.5	7.59E-04
			YLR031W	1.5	9.00E-04
			YDL208W	1.5	1.96E-05
			YOL058W	1.5	1.77E-03
			YOL141W	1.5	1.57E-03
			YMR034C	1.5	3.54E-04
			YGL051W	1.5	8.72E-04

Table S3 continued

			YOR242C	1.5	5.75E-04
			YDR312W	1.5	2.03E-03
			YLL053C	1.5	6.75E-05
			YDL222C	1.5	7.20E-03
			YHR170W	1.5	3.50E-04
			YDR172W	1.5	1.24E-04
			YJR149W	1.5	5.55E-05
			YMR094W	1.5	2.21E-03
			YOL163W	1.5	1.81E-04
			YDR083W	1.5	1.84E-03
			YMR059W	1.5	4.23E-05
			YOL047C	1.5	2.00E-04
			YHL012W	1.5	1.24E-04
			YDL042C	1.5	5.69E-04
			YDR152W	1.5	1.95E-05
			YLR222C	1.5	1.96E-04
			YDL014W	1.5	1.20E-04
			YPL177C	1.5	2.88E-04
			YFL011W	1.5	1.16E-03
			YHR209W	1.5	3.58E-04
			YMR310C	1.5	2.20E-03
			YPL244C	1.5	1.38E-04
			YHR062C	1.5	9.87E-04

Table S3 continued

			YDR038C	1.5	9.37E-05
			YMR242W-A	1.5	1.75E-04
			YNL153C	1.5	1.91E-05
			YBR085C-A	1.5	6.31E-03
			YOR091W	1.5	7.21E-05
			YFL034C-A	1.5	2.35E-04
			YGL125W	1.5	1.44E-04
			YBR271W	1.5	1.97E-03
			YMR074C	1.5	6.16E-05
			YGR123C	1.5	6.56E-05
			YDR120C	1.5	2.21E-04

Table S4 Complete list of differentially expressed genes in *S. cerevisiae* exposed to 1 mg/L nonylphenol (NP) for 120 min

Downregulated			Upregulated		
ORF	**Fold change**	**P-Value**	**ORF**	**Fold change**	**P-Value**
YBR093C	1.7	0.0000	YOL101C	1.6	0.0000
YDR380W	1.7	0.0000	YMR206W	1.6	0.0113
YDL038C	1.6	0.0000	YOR049C	1.5	0.0003
YDL039C	1.6	0.0000	YLR327C	1.5	0.0001
YHR137W	1.5	0.0000	YGR243W	1.5	0.0002
YHR094C	1.5	0.0002	YOR178C	1.4	0.0008
YKL120W	1.4	0.0002	YKL220C	1.4	0.0044
YDL245C	1.4	0.0213	YFL014W	1.4	0.0014
YAR071W	1.4	0.0004	YLR341W	1.4	0.0075
YPR194C	1.4	0.0009	YPR160W	1.4	0.0002
YDL037C	1.4	0.0030	YDR374C	1.4	0.0080
YGL009C	1.4	0.0001	YGL055W	1.3	0.0005
YNL034W	1.3	0.0071	YGR035C	1.3	0.0005
YHR208W	1.3	0.0005	YOL151W	1.3	0.0006
YPL058C	1.3	0.0006	YFR053C	1.3	0.0054
YDR481C	1.3	0.0020	YDR070C	1.3	0.0005
YPL095C	1.2	0.0184	YJR005C-A	1.3	0.0392
YOR032C	1.2	0.0076	YFR015C	1.3	0.0003
YHR136C	1.2	0.0159	YOR153W	1.3	0.0018
YKL029C	1.2	0.0032	YER011W	1.3	0.0010

Table S4 continued

YPL018W	1.2	0.0126	YOR152C	1.3	0.0011
YER028C	1.2	0.0323	YBR117C	1.3	0.0085
YEL069C	1.2	0.0284	YMR196W	1.3	0.0058
YJR149W	1.2	0.0076	YEL011W	1.3	0.0010
YCR098C	1.2	0.0144	YOR040W	1.3	0.0098
YLR089C	1.2	0.0123	YLR099C	1.3	0.0025
YER073W	1.2	0.0034	YDR342C	1.3	0.0010
YDR043C	1.2	0.0136	YLR411W	1.2	0.0177
YJR148W	1.2	0.0037	YHR126C	1.2	0.0304
YGL255W	1.2	0.0038	YBR221W-A	1.2	0.0119
YJR147W	1.2	0.0044	YBR285W	1.2	0.0036
YBL042C	1.2	0.0054	YDR111C	1.2	0.0009
YPL274W	1.2	0.0033	YOL158C	1.2	0.0042
YNL194C	1.2	0.0083	YLR312C	1.2	0.0133
YJL213W	1.2	0.0331	YMR280C	1.2	0.0155
YBL029W	1.2	0.0079	YNL237W	1.2	0.0108
YOL126C	1.2	0.0070	YHR092C	1.2	0.0019
YOR068C	1.2	0.0468	YMR105C	1.2	0.0212
YOL119C	1.2	0.0280	YOR384W	1.2	0.0447
YDR042C	1.2	0.0140	YLR205C	1.2	0.0136
YBL043W	1.1	0.0279	YIL162W	1.2	0.0092
YPR201W	1.1	0.0257	YMR194C-B	1.2	0.0274
YOR221C	1.1	0.0229	YCL073C	1.2	0.0248

Table S4 continued

YOR226C	1.1	0.0219	YNR034W-A	1.2	0.0085
YLR415C	1.1	0.0343	YNL117W	1.2	0.0043
YNL104C	1.1	0.0117	YPL223C	1.2	0.0178
YKR071C	1.1	0.0259	YBR299W	1.2	0.0063
YLR355C	1.1	0.0365	YBL039W-A	1.2	0.0468
YPR035W	1.1	0.0456	YDR223W	1.2	0.0191
YBR068C	1.1	0.0126	YGR201C	1.2	0.0224
YJL056C	1.1	0.0176	YAL062W	1.2	0.0163
YOR190W	1.1	0.0237	YER053C-A	1.2	0.0168
YJR016C	1.1	0.0470	YDR516C	1.2	0.0449
YLR348C	1.1	0.0405	YFL020C	1.2	0.0407
YPL177C	1.1	0.0239	YGR053C	1.2	0.0284
YJL170C	1.1	0.0367	YGR244C	1.2	0.0119
YPL019C	1.1	0.0261	YBR297W	1.2	0.0170
YPR157W	1.1	0.0322	YCL026C-B	1.2	0.0158
YGL035C	1.1	0.0436	YOR289W	1.2	0.0160
YIL119C	1.1	0.0483	YHL035C	1.2	0.0160
YEL017C-A	1.1	0.0430	YOR348C	1.2	0.0233
YLR420W	1.1	0.0365	YFR017C	1.2	0.0123
YGR138C	1.1	0.0391	YGR281W	1.2	0.0168
			YER054C	1.2	0.0253
			YAL060W	1.2	0.0045
			YPR155C	1.2	0.0102

Table S4 continued

			YKL137W	1.2	0.0167
			YMR006C	1.2	0.0462
			YGR230W	1.2	0.0180
			YML042W	1.2	0.0057
			YDR213W	1.2	0.0407
			YIR038C	1.2	0.0276
			YBR298C	1.2	0.0384
			YBR033W	1.2	0.0483
			YKR076W	1.2	0.0341
			YMR090W	1.2	0.0100
			YMR025W	1.2	0.0169
			YMR250W	1.2	0.0189
			YOL166W-A	1.2	0.0313
			YDL169C	1.2	0.0389
			YLR413W	1.2	0.0218
			YML047C	1.2	0.0409
			YDL079C	1.2	0.0335
			YDR448W	1.2	0.0483
			YDL021W	1.2	0.0148
			YNR016C	1.1	0.0347
			YAL046C	1.1	0.0393
			YOL083W	1.1	0.0176
			YOL097W-A	1.1	0.0496

Table S4 continued

			YKL142W	1.1	0.0225
			YDR282C	1.1	0.0431
			YJR096W	1.1	0.0235
			YOL047C	1.1	0.0207
			YGR174C	1.1	0.0293
			YOR173W	1.1	0.0240
			YLR251W	1.1	0.0468
			YGL039W	1.1	0.0169
			YOR100C	1.1	0.0240
			YLR177W	1.1	0.0255
			YBL005W	1.1	0.0305
			YJL196C	1.1	0.0216
			YIR028W	1.1	0.0229
			YPL231W	1.1	0.0477
			YKL217W	1.1	0.0265
			YER150W	1.1	0.0368
			YJL052W	1.1	0.0403
			YDR019C	1.1	0.0203
			YDR275W	1.1	0.0206
			YMR135C	1.1	0.0441
			YER142C	1.1	0.0435
			YDL181W	1.1	0.0260
			YKL182W	1.1	0.0391

Table S4 continued

			YNL014W	1.1	0.0253
			YKL026C	1.1	0.0246
			YPL113C	1.1	0.0460
			YFR014C	1.1	0.0387
			YDR277C	1.1	0.0378
			YER018C	1.1	0.0395
			YNL274C	1.1	0.0428
			YMR145C	1.1	0.0490
			YHR171W	1.1	0.0454
			YDR243C	1.1	0.0480
			YLR070C	1.1	0.0330
			YBR230C	1.1	0.0452

Table S5 Complete list of differentially expressed genes in *S. cerevisiae* exposed to 1 mg/L nonylphenol (NP) for 180 min

Downregulated			Upregulated		
ORF	**Fold change**	**P-Value**	**ORF**	**Fold change**	**P-Value**
YPR194C	1.5	0.0004	YOR049C	1.5	0.0000
YPL095C	1.4	0.0003	YOL152W	1.5	0.0053
YDR380W	1.4	0.0012	YGR035C	1.5	0.0016
YIL160C	1.4	0.0076	YOR178C	1.4	0.0008
YHR212W-A	1.4	0.0323	YPL111W	1.3	0.0015
YBR072C-A	1.4	0.0336	YOR152C	1.3	0.0003
YJL213W	1.3	0.0113	YLR214W	1.3	0.0158
YDL037C	1.3	0.0056	YDR111C	1.3	0.0011
YBR093C	1.3	0.0306	YPR124W	1.3	0.0146
YNL018C	1.3	0.0042	YML047C	1.3	0.0205
YDL039C	1.3	0.0053	YKR046C	1.2	0.0016
YLL057C	1.3	0.0049	YEL065W	1.2	0.0107
YEL069C	1.3	0.0079	YBR200W-A	1.2	0.0479
YIL060W	1.3	0.0344	YOL151W	1.2	0.0205
YKL070W	1.3	0.0419	YOR384W	1.2	0.0452
YOR032C	1.3	0.0044	YJL116C	1.2	0.0222
YHR137W	1.3	0.0244	YGL192W	1.2	0.0306
YNL269W	1.2	0.0475	YNR071C	1.2	0.0401
YLR377C	1.2	0.0428	YLR327C	1.2	0.0250
YLR130C	1.2	0.0372	YOR153W	1.2	0.0049

Table S5 continued

YJR149W	1.2	0.0081	YJL026W	1.2	0.0200
YBL042C	1.2	0.0059	YBR148W	1.2	0.0406
YLR364W	1.2	0.0131	YPR159C-A	1.2	0.0319
YHR213W-A	1.2	0.0203	YER011W	1.2	0.0504
YOL156W	1.2	0.0464	YJR005C-A	1.2	0.0359
YCR104W	1.2	0.0056	YIL101C	1.2	0.0344
YDR003W-A	1.2	0.0131	YNL237W	1.2	0.0393
YDR379C-A	1.2	0.0268	YAR035C-A	1.2	0.0234
YJR148W	1.2	0.0045	YDR534C	1.2	0.0296
YLR348C	1.2	0.0221	YLR099C	1.2	0.0132
YHR094C	1.2	0.0242	YKL093W	1.2	0.0413
YCR098C	1.2	0.0151	YPL156C	1.2	0.0167
YGL188C-A	1.2	0.0095	YNR044W	1.2	0.0283
YBR151W	1.2	0.0427	YLR411W	1.2	0.0159
YDR481C	1.2	0.0281	YPL017C	1.2	0.0398
YNR069C	1.2	0.0447	YLR438W	1.2	0.0399
YMR120C	1.2	0.0306	YKL143W	1.1	0.0251
YHR136C	1.2	0.0254	YDR361C	1.1	0.0390
YGL255W	1.2	0.0217	YBR299W	1.1	0.0290
YPL274W	1.2	0.0173	YNL112W	1.1	0.0471
YOR226C	1.1	0.0197	YMR058W	1.1	0.0261
YER069W	1.1	0.0373	YOL091W	1.1	0.0260
YOL126C	1.1	0.0308	YJL010C	1.1	0.0360

Table S5 continued

YLR089C	1.1	0.0303	YOR374W	1.1	0.0397
YER073W	1.1	0.0387	YGR075C	1.1	0.0293
YOR273C	1.1	0.0287	YMR105C	1.1	0.0342
YIL121W	1.1	0.0427	YBR066C	1.1	0.0476
YGR138C	1.1	0.0256			
YNL065W	1.1	0.0411			
YLR148W	1.1	0.0419			
YCR107W	1.1	0.0426			
YOL119C	1.1	0.0367			
YPR002W	1.1	0.0397			
YMR158C-A	1.1	0.0480			
YIL088C	1.1	0.0410			
YJL051W	1.1	0.0438			

Table S6 Complete list of differentially expressed genes in *S. cerevisiae* exposed to 5 mg/L nonylphenol (NP) for 120 min

Downregulated			Upregulated		
ORF	**Fold change**	**P-Value**	**ORF**	**Fold change**	**P-Value**
YPR194C	4.0	3.23E-07	YER106W	23.2	3.51E-11
YBR084W	2.6	3.00E-08	YLR307C-A	16.9	1.37E-11
YHR092C	2.4	4.62E-08	YGR059W	9.9	1.20E-09
YDR380W	2.4	5.27E-08	YGR035C	9.0	2.72E-11
YGR138C	2.4	1.69E-07	YHR079C-A	8.2	1.38E-07
YMR290C	2.3	2.14E-07	YJL153C	8.2	5.79E-08
YHR137W	2.3	1.11E-07	YGL032C	7.9	9.57E-10
YMR229C	2.1	6.01E-07	YJR005C-A	7.6	3.39E-10
YHL028W	2.0	3.70E-06	YLR412C-A	6.8	1.75E-09
YGR159C	2.0	2.64E-07	YPL130W	6.6	5.80E-09
YOR269W	2.0	7.85E-06	YOR134W	6.3	8.21E-08
YOR239W	2.0	8.89E-07	YHR139C	6.2	3.10E-10
YML056C	1.9	5.52E-07	YBR056W-A	6.0	1.73E-07
YGR123C	1.9	3.58E-07	YFL014W	5.9	1.96E-09
YHR049W	1.9	2.45E-06	YMR251W	5.6	4.87E-09
YHR032W	1.9	6.05E-06	YLL046C	5.4	2.51E-08
YJL212C	1.9	2.66E-05	YPR151C	5.0	6.03E-09
YKR036C	1.8	6.07E-07	YNL145W	5.0	7.11E-08
YOR204W	1.8	7.13E-05	YPL021W	4.7	4.25E-07
YDR514C	1.8	6.12E-07	YMR107W	4.7	1.14E-06

Table S6 continued

YPL274W	1.8	6.84E-07	YGR236C	4.7	5.06E-09
YOL141W	1.8	3.28E-06	YGR273C	4.6	5.37E-08
YBR093C	1.8	2.40E-06	YOL052C-A	4.4	5.33E-07
YDR440W	1.8	5.08E-06	YDR070C	4.4	8.53E-09
YLR420W	1.8	3.88E-06	YBR284W	4.0	3.31E-09
YBL042C	1.8	2.85E-06	YHL022C	4.0	2.32E-09
YDR299W	1.8	2.84E-06	YHR096C	4.0	5.07E-07
YIL119C	1.8	2.31E-04	YMR101C	3.9	2.93E-09
YOR217W	1.8	3.39E-06	YIL015W	3.9	2.74E-08
YBL029W	1.8	2.69E-06	YBR072C-A	3.9	7.48E-08
YLR452C	1.8	1.37E-06	YKL107W	3.8	1.39E-07
YER060W	1.8	3.05E-06	YGL156W	3.7	6.78E-08
YGL016W	1.8	1.56E-06	YMR133W	3.7	5.28E-08
YPL183C	1.8	8.63E-06	YLR081W	3.7	2.31E-06
YDL205C	1.8	1.47E-06	YLR099C	3.6	3.77E-09
YDR342C	1.7	6.37E-06	YLR327C	3.6	3.73E-08
YKL014C	1.7	2.67E-06	YGR161C	3.6	1.96E-08
YJL122W	1.7	8.84E-06	YLR136C	3.5	5.00E-07
YDR234W	1.7	2.26E-06	YKR046C	3.4	1.58E-06
YKL120W	1.7	1.67E-05	YOR154W	3.4	4.89E-09
YOR273C	1.7	8.67E-06	YPL250C	3.4	3.38E-08
YBL097W	1.7	1.85E-05	YOR178C	3.4	3.78E-07
YDL181W	1.7	4.01E-06	YAL061W	3.4	2.96E-06

Table S6 continued

YIL121W	1.7	2.92E-06	YDR171W	3.3	3.75E-08
YPR010C	1.7	3.15E-06	YOR382W	3.2	3.69E-08
YGR068C	1.7	6.19E-06	YLL042C	3.2	6.38E-09
YMR230W-A	1.7	3.49E-04	YLR346C	3.2	5.79E-08
YMR199W	1.7	1.66E-04	YIL101C	3.2	1.62E-06
YMR117C	1.7	5.42E-06	YHR176W	3.2	1.54E-08
YBR184W	1.7	2.40E-05	YMR013W-A	3.2	2.69E-06
YCR065W	1.7	5.45E-05	YHL047C	3.2	1.58E-08
YER001W	1.7	2.02E-06	YMR175W	3.2	8.56E-07
YOR341W	1.7	4.60E-06	YLR205C	3.1	1.80E-07
YBR263W	1.7	5.02E-05	YBR018C	3.1	2.02E-08
YKL216W	1.7	9.82E-06	YIL066C	3.1	8.60E-08
YIL085C	1.7	4.60E-06	YPL027W	3.0	2.70E-06
YDR399W	1.7	9.76E-06	YBL078C	3.0	5.49E-07
YJR053W	1.6	1.40E-04	YJL133C-A	3.0	4.20E-08
YIL079C	1.6	1.30E-05	YEL070W	3.0	3.51E-08
YDR321W	1.6	3.67E-05	YEL065W	3.0	5.71E-08
YBR021W	1.6	6.33E-05	YHR138C	3.0	1.88E-07
YGR004W	1.6	5.94E-05	YLR070C	2.9	1.10E-08
YLR083C	1.6	4.00E-06	YNL077W	2.9	1.01E-08
YNL026W	1.6	2.39E-06	YGL121C	2.9	3.09E-08
YOR243C	1.6	4.68E-06	YOL047C	2.9	1.74E-07
YGL142C	1.6	4.09E-06	YGL015C	2.9	1.39E-05

Table S6 continued

YDL211C	1.6	3.48E-05	YOR072W-B	2.9	2.77E-08
YCR075C	1.6	5.57E-05	YOR049C	2.9	1.77E-07
YOL007C	1.6	2.41E-04	YBR072W	2.9	5.70E-07
YGR071C	1.6	8.89E-06	YMR317W	2.9	1.44E-06
YGR221C	1.6	1.58E-04	YGR142W	2.8	2.87E-07
YJL181W	1.6	5.45E-06	YER103W	2.8	7.69E-08
YPL226W	1.6	1.15E-05	YDR406W	2.8	6.47E-07
YLR342W-A	1.6	8.47E-06	YML058W-A	2.7	4.38E-07
YEL029C	1.6	2.76E-05	YBR298C-A	2.7	3.57E-04
YBR187W	1.6	7.64E-05	YNL036W	2.7	1.55E-07
YBR271W	1.6	8.05E-05	YFR032C	2.7	5.22E-06
YMR131C	1.6	3.41E-05	YGR243W	2.7	1.82E-07
YMR308C	1.6	7.03E-06	YLR281C	2.7	2.95E-07
YEL055C	1.6	4.61E-06	YJR120W	2.6	1.36E-05
YGR108W	1.6	4.99E-05	YOR384W	2.6	9.82E-08
YGR116W	1.6	2.04E-05	YLR142W	2.6	1.38E-07
YNR055C	1.6	1.42E-05	YJL116C	2.6	6.41E-06
YNL132W	1.6	1.40E-05	YBR147W	2.6	1.81E-08
YOR038C	1.6	5.62E-06	YBR066C	2.6	1.95E-08
YPL122C	1.6	1.21E-05	YPR002W	2.6	3.52E-07
YJR054W	1.6	8.08E-06	YDR523C	2.6	5.31E-06
YJL187C	1.6	2.21E-05	YLR267W	2.6	5.33E-07
YJR002W	1.6	5.21E-06	YIL099W	2.6	6.94E-07

Table S6 continued

YER086W	1.6	2.19E-05	YLR031W	2.6	1.29E-05
YLR343W	1.6	2.59E-05	YER150W	2.5	8.84E-08
YPL263C	1.6	5.70E-06	YCR010C	2.5	4.17E-06
YDR144C	1.6	8.49E-05	YDR534C	2.5	4.55E-06
YCL037C	1.6	1.07E-04	YLR411W	2.5	4.50E-08
YOR071C	1.6	1.75E-05	YML054C	2.5	2.37E-08
YBR074W	1.6	1.54E-05	YOL151W	2.5	3.38E-07
YHR025W	1.6	5.39E-06	YBL049W	2.5	6.55E-07
YBR104W	1.6	1.38E-04	YNL237W	2.5	3.48E-07
YHR047C	1.6	2.38E-05	YPL054W	2.5	3.95E-07
YGR109C	1.6	2.86E-04	YDR516C	2.5	5.72E-08
YHR019C	1.6	9.22E-06	YER104W	2.5	9.17E-08
YDL240W	1.6	2.82E-04	YHL040C	2.5	7.64E-06
YDR020C	1.6	5.19E-04	YML128C	2.5	9.44E-07
YOL125W	1.6	1.82E-05	YDL169C	2.4	7.59E-08
YOL098C	1.6	3.39E-05	YDR461W	2.4	1.24E-07
YGR090W	1.6	1.45E-05	YPL033C	2.4	2.12E-07
YLR460C	1.5	1.84E-04	YLR030W	2.4	6.65E-05
YMR182W-A	1.5	5.90E-05	YGR248W	2.4	1.00E-06
YNL218W	1.5	2.48E-05	YHR086W-A	2.4	9.51E-06
YCL030C	1.5	6.40E-06	YOR351C	2.4	3.85E-05
YLR129W	1.5	5.09E-06	YBR117C	2.4	2.47E-06
YHR169W	1.5	1.14E-04	YIL134C-A	2.4	1.69E-05

Table S6 continued

YGR006W	1.5	4.72E-05	YNR034W	2.4	2.16E-07
YNL034W	1.5	9.61E-04	YHR087W	2.4	5.39E-07
YBR092C	1.5	1.78E-05	YNL195C	2.4	1.14E-07
YDR420W	1.5	9.29E-05	YDR258C	2.4	1.20E-07
YHR031C	1.5	3.03E-05	YGR146C-A	2.4	2.03E-07
YNL182C	1.5	8.69E-05	YGR043C	2.4	2.24E-07
YOR323C	1.5	6.30E-06	YNL194C	2.3	9.36E-06
YOR313C	1.5	2.57E-05	YOL158C	2.3	8.45E-08
YJR031C	1.5	9.68E-06	YDR194W-A	2.3	2.08E-06
YFL004W	1.5	1.12E-05	YOR173W	2.3	8.73E-08
YDL209C	1.5	3.38E-05	YGR201C	2.3	3.45E-07
YGR040W	1.5	1.39E-05	YJL144W	2.3	4.69E-07
YER089C	1.5	2.22E-05	YOL155W-A	2.3	4.22E-06
YDR324C	1.5	1.44E-04	YDL085W	2.3	9.74E-06
YGL077C	1.5	1.73E-05	YJL136W-A	2.3	1.55E-04
YEL054C	1.5	3.77E-04	YBR285W	2.3	2.86E-07
YPL245W	1.5	1.94E-04	YKR097W	2.3	1.12E-07
YMR163C	1.5	5.40E-04	YBR006W	2.3	1.57E-07
YOL076W	1.5	1.08E-04	YKR011C	2.3	1.11E-07
YLR384C	1.5	2.33E-05	YDL173W	2.3	1.30E-07
YJL186W	1.5	5.20E-05	YDR384C	2.3	5.27E-07
YOR073W	1.5	6.35E-05	YOR183W	2.3	1.40E-05
YPL279C	1.5	1.21E-05	YOL155C	2.2	1.59E-06

Table S6 continued

YBR220C	1.5	1.05E-05	YPR015C	2.2	2.66E-05
YNL062C	1.5	4.19E-05	YDR403W	2.2	1.87E-06
YPR083W	1.5	3.91E-05	YPR184W	2.2	3.28E-07
YOR296W	1.5	9.65E-06	YEL060C	2.2	2.57E-06
YPL112C	1.5	1.93E-05	YIL055C	2.2	3.52E-07
YER073W	1.5	1.15E-05	YER037W	2.2	2.49E-06
YPL063W	1.5	1.73E-05	YJR095W	2.2	2.29E-06
YGL009C	1.5	1.61E-05	YGR144W	2.2	1.19E-06
YOL126C	1.5	1.20E-05	YMR323W	2.2	1.62E-05
YER055C	1.5	5.97E-04	YOR152C	2.2	8.23E-07
YER118C	1.5	1.68E-05	YGL205W	2.2	1.80E-06
YPL082C	1.5	3.13E-05	YOR394W	2.2	1.07E-04
YDL227C	1.5	1.20E-04	YOR383C	2.2	1.65E-06
YGL083W	1.5	2.06E-04	YGL179C	2.2	3.92E-07
YLR342W	1.5	1.25E-04	YOR237W	2.2	1.10E-06
YOL122C	1.5	2.18E-05	YBR294W	2.2	5.03E-04
YBR025C	1.5	1.38E-05	YGR066C	2.2	6.21E-06
YDR106W	1.5	1.62E-02	YOR374W	2.2	2.28E-06
YLL048C	1.5	2.36E-05	YNR034W-A	2.2	2.49E-06
YDR156W	1.5	9.42E-05	YOR289W	2.1	7.35E-07
YLR143W	1.5	1.91E-05	YHR124W	2.1	3.49E-07
YHR064C	1.5	1.72E-04	YPL230W	2.1	1.50E-05
YPR060C	1.5	4.68E-04	YGR224W	2.1	2.68E-04

Table S6 continued

YMR012W	1.5	8.58E-05	YBR047W	2.1	2.96E-06
YKR093W	1.5	3.59E-04	YJL170C	2.1	2.81E-06
YKR079C	1.5	2.97E-05	YNL277W-A	2.1	2.49E-07
YIL096C	1.5	2.70E-04	YLR312C	2.1	1.53E-06
YNL112W	1.5	1.63E-05	YGR109W-A	2.1	3.49E-04
YHL018W	1.5	1.62E-04	YIL155C	2.1	1.24E-06
YDR060W	1.5	5.32E-05	YIL169C	2.1	8.47E-06
YGR200C	1.5	1.57E-05	YGR213C	2.1	3.16E-05
YNL125C	1.5	9.04E-04	YHL035C	2.1	6.26E-07
YMR098C	1.5	2.47E-05	YDL223C	2.1	1.90E-06
			YMR196W	2.1	3.91E-06
			YMR322C	2.1	1.86E-06
			YNL037C	2.1	2.50E-06
			YDL114W	2.1	1.83E-05
			YPR094W	2.1	1.13E-06
			YDR270W	2.1	1.77E-07
			YHR126C	2.1	1.53E-04
			YKL071W	2.1	1.19E-05
			YBR085C-A	2.1	5.30E-06
			YPL088W	2.0	1.82E-06
			YLR178C	2.0	7.80E-07
			YNL277W	2.0	6.45E-07
			YML118W	2.0	4.31E-07

Table S6 continued

			YMR174C	2.0	1.02E-06
			YNL212W	2.0	3.02E-07
			YGL051W	2.0	2.74E-06
			YPL247C	2.0	2.46E-06
			YKR076W	2.0	9.64E-07
			YEL069C	2.0	3.06E-04
			YOR268C	2.0	7.52E-07
			YDR453C	2.0	2.96E-07
			YDR218C	2.0	1.69E-04
			YJR008W	2.0	8.58E-07
			YIL070C	2.0	1.51E-06
			YGR146C	2.0	2.89E-06
			YER054C	2.0	2.12E-05
			YLR149C	2.0	1.19E-05
			YJL049W	2.0	8.82E-07
			YMR206W	2.0	1.33E-04
			YPL201C	2.0	8.12E-06
			YIR039C	2.0	4.00E-06
			YIL172C	2.0	8.00E-06
			YFR023W	2.0	2.76E-04
			YOL156W	2.0	5.63E-06
			YEL039C	2.0	9.80E-07
			YAL060W	2.0	5.97E-07

Table S6 continued

			YLR154C-H	2.0	1.01E-05
			YBR301W	2.0	5.46E-07
			YHR177W	2.0	5.10E-05
			YJL219W	1.9	2.73E-06
			YIL056W	1.9	1.29E-05
			YBR296C	1.9	2.39E-05
			YCR021C	1.9	6.38E-05
			YLR194C	1.9	5.94E-06
			YKL106C-A	1.9	1.38E-04
			YAR071W	1.9	9.10E-07
			YMR011W	1.9	7.74E-06
			YKL142W	1.9	2.44E-05
			YGL021W	1.9	4.15E-07
			YFR017C	1.9	1.71E-05
			YHR094C	1.9	7.85E-06
			YNL075W	1.9	4.41E-07
			YDL021W	1.9	8.05E-07
			YMR040W	1.9	2.64E-06
			YIL176C	1.9	2.91E-07
			YER179W	1.9	2.39E-05
			YPL051W	1.9	4.59E-06
			YNL014W	1.9	5.43E-07
			YOR185C	1.9	3.41E-06

Table S6 continued

			YGL037C	1.9	4.55E-06
			YFL040W	1.9	3.88E-04
			YMR181C	1.9	1.39E-05
			YER145C	1.9	1.12E-06
			YOR214C	1.9	3.66E-06
			YDR253C	1.9	2.21E-06
			YBL005W	1.9	4.62E-07
			YCR089W	1.9	4.46E-06
			YMR105C	1.9	4.81E-05
			YIL045W	1.9	1.71E-06
			YPL223C	1.9	2.17E-06
			YOR360C	1.9	1.39E-06
			YDL178W	1.9	1.49E-06
			YJL089W	1.9	6.25E-05
			YNL231C	1.9	1.09E-06
			YMR102C	1.9	1.89E-06
			YPL017C	1.9	7.06E-06
			YLL026W	1.9	5.22E-06
			YAL068C	1.9	1.70E-06
			YML083C	1.9	3.87E-05
			YNL160W	1.9	1.91E-04
			YHR179W	1.9	7.60E-07
			YIL107C	1.9	6.88E-07

Table S6 continued

			YPL111W	1.9	3.06E-06
			YNL093W	1.9	7.28E-07
			YOL022C	1.9	4.01E-06
			YGR256W	1.8	4.35E-06
			YJL161W	1.8	1.44E-05
			YAR035W	1.8	3.42E-05
			YPR159C-A	1.8	4.68E-04
			YGL006W-A	1.8	8.76E-04
			YPR108W-A	1.8	4.97E-05
			YDR082W	1.8	4.69E-06
			YML100W	1.8	3.06E-05
			YDR522C	1.8	3.89E-04
			YKL163W	1.8	1.81E-05
			YOL051W	1.8	1.45E-05
			YOR192C-C	1.8	9.04E-06
			YDL020C	1.8	5.21E-07
			YOR153W	1.8	5.29E-06
			YBR214W	1.8	1.22E-04
			YGR110W	1.8	1.65E-06
			YGR019W	1.8	3.11E-06
			YBL108C-A	1.8	1.46E-06
			YDR256C	1.8	2.02E-05
			YBR076W	1.8	1.23E-04

Table S6 continued

			YCL044C	1.8	1.17E-05
			YEL011W	1.8	2.34E-06
			YDL182W	1.8	4.88E-07
			YPL061W	1.8	3.11E-06
			YPL186C	1.8	1.06E-06
			YKL221W	1.8	3.10E-06
			YGR212W	1.8	7.86E-06
			YOR136W	1.8	4.66E-06
			YIL082W-A	1.8	2.44E-04
			YGR008C	1.8	1.59E-05
			YDL124W	1.8	3.96E-06
			YBL043W	1.8	2.29E-05
			YLL039C	1.8	7.62E-05
			YOL084W	1.8	1.61E-06
			YBR208C	1.8	1.39E-06
			YGR109W-B	1.8	1.45E-04
			YMR041C	1.8	1.39E-06
			YDR034W-B	1.8	1.95E-04
			YCL040W	1.8	6.25E-05
			YLR377C	1.8	6.34E-04
			YGR174W-A	1.8	1.14E-03
			YHR027C	1.7	1.57E-06
			YOL083W	1.7	1.88E-06

Table S6 continued

			YLR461W	1.7	9.92E-07
			YOL162W	1.7	2.94E-05
			YJR091C	1.7	3.20E-05
			YOR019W	1.7	8.59E-06
			YKL070W	1.7	5.80E-05
			YPL038W-A	1.7	1.93E-04
			YKR049C	1.7	2.49E-06
			YBR148W	1.7	2.43E-06
			YDR074W	1.7	5.24E-06
			YAL012W	1.7	4.41E-06
			YFL031W	1.7	5.64E-05
			YAL002W	1.7	1.99E-06
			YOR208W	1.7	1.30E-05
			YOL036W	1.7	1.82E-06
			YJR079W	1.7	1.20E-04
			YMR316W	1.7	1.16E-05
			YML092C	1.7	4.24E-06
			YJR078W	1.7	1.84E-06
			YNL318C	1.7	1.10E-04
			YPL159C	1.7	3.46E-06
			YCL039W	1.7	1.49E-05
			YNR069C	1.7	4.22E-06
			YOL010W	1.7	2.86E-06

Table S6 continued

			YPL265W	1.7	3.13E-05
			YOR357C	1.7	1.16E-05
			YCL069W	1.7	1.06E-03
			YJL047C-A	1.7	1.82E-06
			YML130C	1.7	2.32E-06
			YMR090W	1.7	5.09E-06
			YGR239C	1.7	1.88E-06
			YDL054C	1.7	7.28E-06
			YNL208W	1.7	2.06E-06
			YOR120W	1.7	3.93E-06
			YBR126C	1.7	2.24E-05
			YIL136W	1.7	1.01E-05
			YHR140W	1.7	2.57E-06
			YLR080W	1.7	4.75E-06
			YLR284C	1.7	5.65E-06
			YLL023C	1.7	2.86E-05
			YJR085C	1.7	2.16E-05
			YDR246W-A	1.7	5.59E-05
			YLR054C	1.7	3.95E-05
			YGR131W	1.7	6.33E-05
			YMR291W	1.7	1.12E-04
			YGR249W	1.7	1.11E-04
			YIL113W	1.7	2.92E-05

Table S6 continued

			YBL101W-A	1.7	1.18E-04
			YHR214C-E	1.7	4.32E-03
			YAL062W	1.7	7.35E-05
			YOL131W	1.7	1.03E-03
			YDR223W	1.7	5.81E-05
			YAL067W-A	1.7	4.51E-03
			YPL260W	1.7	2.52E-06
			YNL042W-B	1.7	8.08E-06
			YLR177W	1.7	2.28E-06
			YNL117W	1.7	1.27E-05
			YKL183C-A	1.7	5.34E-04
			YPL135W	1.7	1.97E-06
			YMR118C	1.7	8.45E-04
			YIL160C	1.7	9.89E-04
			YJR073C	1.7	2.30E-05
			YCR104W	1.7	1.12E-04
			YGL062W	1.7	7.96E-06
			YKL151C	1.7	6.23E-06
			YML034W	1.7	4.69E-06
			YCR005C	1.7	2.29E-05
			YER142C	1.7	1.02E-05
			YOR255W	1.7	3.80E-04
			YGL244W	1.7	7.24E-06

Table S6 continued

			YDL130W-A	1.7	3.59E-05
			YMR058W	1.7	4.24E-06
			YDL215C	1.7	4.81E-06
			YPR040W	1.7	1.11E-05
			YDL222C	1.7	5.32E-04
			YMR194C-B	1.7	6.46E-05
			YOR316C	1.7	7.53E-06
			YNL269W	1.7	2.89E-04
			YBR071W	1.7	4.67E-05
			YHL024W	1.7	4.84E-04
			YOR328W	1.7	3.20E-06
			YHR038W	1.7	2.11E-06
			YOL113W	1.6	3.78E-05
			YPL171C	1.6	2.04E-03
			YPR124W	1.6	3.27E-06
			YOR344C	1.6	8.55E-05
			YIR038C	1.6	8.50E-05
			YBR212W	1.6	1.14E-04
			YLR275W	1.6	7.51E-05
			YBR033W	1.6	3.76E-05
			YOL016C	1.6	3.73E-05
			YMR250W	1.6	8.13E-06
			YGL138C	1.6	3.55E-03

Table S6 continued

			YKR039W	1.6	2.49E-05
			YDL024C	1.6	1.28E-05
			YJR044C	1.6	4.04E-06
			YDL110C	1.6	4.71E-05
			YCR077C	1.6	8.76E-06
			YBL039W-A	1.6	1.48E-04
			YLL064C	1.6	2.60E-06
			YKL164C	1.6	4.42E-05
			YGL157W	1.6	2.09E-05
			YDL244W	1.6	3.64E-05
			YOR385W	1.6	1.54E-05
			YNL274C	1.6	8.99E-06
			YPL264C	1.6	3.23E-06
			YOL132W	1.6	1.88E-04
			YPL222W	1.6	3.13E-06
			YNL146C-A	1.6	2.05E-05
			YFL016C	1.6	5.92E-06
			YGL020C	1.6	1.10E-05
			YER078W-A	1.6	8.55E-04
			YDR358W	1.6	2.95E-04
			YGL228W	1.6	2.74E-06
			YER069W	1.6	1.52E-05
			YHL021C	1.6	5.50E-05

Table S6 continued

			YOR252W	1.6	7.39E-05
			YPR001W	1.6	7.30E-05
			YER079W	1.6	3.29E-05
			YDR374C	1.6	9.12E-04
			YJL026W	1.6	3.72E-05
			YGR174C	1.6	8.88E-06
			YCL012C	1.6	4.93E-06
			YOR052C	1.6	8.95E-06
			YDL204W	1.6	1.06E-03
			YOR036W	1.6	1.84E-05
			YPR036W-A	1.6	5.44E-06
			YIL046W-A	1.6	1.83E-04
			YIL158W	1.6	5.57E-05
			YHR143W	1.6	6.87E-05
			YER053C-A	1.6	2.61E-05
			YLR370C	1.6	2.73E-05
			YCR061W	1.6	4.07E-04
			YGR087C	1.6	7.68E-05
			YBL005W-A	1.6	6.70E-04
			YNL200C	1.6	5.45E-06
			YDL022W	1.6	6.63E-05
			YNL027W	1.6	4.12E-05
			YJL070C	1.6	1.29E-05

Table S6 continued

			YDR259C	1.6	2.53E-05
			YCR020C	1.6	4.28E-05
			YDR013W	1.6	1.12E-04
			YBR169C	1.6	2.15E-05
			YOR100C	1.6	8.20E-05
			YGR023W	1.6	2.77E-04
			YER183C	1.6	2.05E-04
			YPR030W	1.6	3.52E-04
			YNL070W	1.6	3.31E-04
			YJR150C	1.6	2.00E-03
			YER044C-A	1.6	5.09E-04
			YNL305C	1.6	1.03E-05
			YMR169C	1.6	1.71E-04
			YIL037C	1.6	8.93E-04
			YLR406C-A	1.6	8.60E-04
			YNL100W	1.6	6.60E-06
			YGL258W-A	1.6	9.64E-04
			YPL188W	1.6	1.29E-05
			YHR054C	1.6	3.78E-05
			YOL154W	1.6	5.20E-05
			YGL209W	1.6	9.37E-06
			YBR062C	1.6	8.71E-05
			YOR023C	1.6	2.38E-04

Table S6 continued

			YJL030W	1.6	9.38E-06
			YDR019C	1.5	3.12E-05
			YEL012W	1.5	2.52E-05
			YMR085W	1.5	4.86E-05
			YKL193C	1.5	1.29E-05
			YJL155C	1.5	8.99E-06
			YMR309C	1.5	1.09E-05
			YOL087C	1.5	7.47E-06
			YHR014W	1.5	3.15E-04
			YIR014W	1.5	2.40E-04
			YDR177W	1.5	8.53E-06
			YEL047C	1.5	2.20E-05
			YMR202W	1.5	5.23E-05
			YML015C	1.5	8.35E-06
			YMR195W	1.5	1.66E-05
			YGL073W	1.5	4.22E-05
			YJL126W	1.5	2.56E-04
			YGR180C	1.5	5.80E-05
			YNR019W	1.5	6.93E-04
			YER175C	1.5	1.09E-05
			YIL135C	1.5	2.54E-04
			YPL156C	1.5	1.64E-05
			YGR075C	1.5	7.62E-06

Table S6 continued

			YER067W	1.5	6.41E-05
			YPL164C	1.5	3.45E-05
			YLR254C	1.5	3.82E-05
			YBR269C	1.5	1.01E-05
			YGL183C	1.5	1.08E-03
			YJR010W	1.5	5.36E-05
			YBL050W	1.5	9.17E-04
			YJR151W-A	1.5	1.20E-03
			YJL171C	1.5	8.01E-05
			YKL124W	1.5	7.12E-05
			YGR076C	1.5	3.73E-05
			YOL023W	1.5	2.02E-05
			YJL082W	1.5	8.50E-05
			YDL174C	1.5	1.25E-05
			YAL055W	1.5	1.38E-05
			YNR068C	1.5	2.28E-05
			YKL026C	1.5	1.90E-05
			YGR062C	1.5	6.85E-05
			YBR207W	1.5	2.42E-05
			YDR195W	1.5	4.61E-05
			YJR059W	1.5	2.15E-05
			YLR201C	1.5	1.79E-05
			YPR157W	1.5	1.25E-05

Table S6 continued

			YHR209W	1.5	1.21E-05
			YMR104C	1.5	1.26E-04
			YBR019C	1.5	2.76E-03
			YBR016W	1.5	9.98E-05
			YOR150W	1.5	8.77E-05
			YLR053C	1.5	4.51E-04
			YBR067C	1.5	4.95E-05

Table S7 Complete list of differentially expressed genes in *S. cerevisiae* exposed to 5 mg/L nonylphenol (NP) for 180 min

Downregulated			Upregulated		
ORF	**Fold change**	**P-Value**	**ORF**	**Fold change**	**P-Value**
YPR194C	7.1	1.28E-08	YLR307C-A	15.0	8.53E-09
YDR380W	3.8	4.61E-08	YER106W	12.9	2.86E-07
YHR092C	3.1	2.07E-08	YJR005C-A	12.7	1.17E-09
YHR137W	2.9	2.56E-07	YGR035C	10.6	1.25E-09
YGR138C	2.5	1.20E-07	YMR251W	7.0	2.20E-08
YMR230W-A	2.4	2.87E-04	YMR317W	6.4	1.62E-06
YGR108W	2.4	5.82E-07	YNL145W	6.4	1.57E-07
YBR184W	2.3	2.08E-06	YGL032C	5.9	1.78E-06
YIL121W	2.3	1.48E-07	YJL153C	5.6	7.70E-08
YDL181W	2.3	2.75E-07	YLR136C	5.5	1.91E-08
YOR313C	2.2	2.06E-05	YGR059W	5.1	2.38E-07
YDR342C	2.2	1.26E-06	YDR534C	5.1	2.93E-07
YCR075C	2.2	4.89E-06	YHL047C	4.8	9.23E-09
YBR084W	2.2	1.67E-07	YHR139C	4.8	4.14E-09
YOR273C	2.2	4.49E-07	YBR056W-A	4.8	1.51E-06
YOL143C	2.1	1.77E-06	YLR412C-A	4.8	1.19E-06
YLR420W	2.1	1.51E-06	YOR382W	4.7	1.40E-08
YOR032C	2.1	6.45E-07	YEL065W	4.5	8.22E-09
YER055C	2.0	1.16E-05	YHL040C	4.5	9.64E-08
YBL042C	2.0	2.91E-07	YGR236C	4.5	2.02E-08

Table S7 continued

YKL216W	2.0	1.45E-06	YJL116C	4.5	1.61E-06
YPL095C	2.0	5.09E-07	YIL101C	4.4	5.61E-08
YOR269W	1.9	1.14E-05	YPL130W	4.4	1.38E-08
YNR004W	1.9	1.12E-05	YHR079C-A	4.4	1.40E-07
YHL028W	1.9	8.58E-06	YGR161C	4.4	5.13E-09
YPL274W	1.9	5.89E-07	YOR134W	4.3	5.49E-08
YJL102W	1.9	1.94E-05	YPL021W	4.3	2.80E-07
YJR048W	1.9	1.54E-05	YOR384W	4.2	6.87E-07
YOL126C	1.9	4.26E-06	YML058W-A	4.2	1.07E-06
YNL126W	1.8	4.00E-06	YHR094C	4.1	2.66E-08
YML056C	1.8	1.08E-06	YAL061W	4.0	1.45E-07
YPR156C	1.8	3.12E-03	YIL015W	4.0	2.63E-09
YJR010C-A	1.8	2.02E-05	YPL250C	3.9	3.07E-08
YDR529C	1.8	3.16E-05	YHR096C	3.9	6.31E-07
YEL029C	1.8	5.25E-06	YLR346C	3.7	7.99E-07
YDR377W	1.8	6.84E-06	YMR107W	3.6	1.06E-06
YLR264W	1.8	2.99E-05	YKR046C	3.6	4.67E-07
YCR020W-B	1.8	1.15E-05	YOL052C-A	3.5	9.96E-08
YPR027C	1.8	6.01E-05	YDR406W	3.5	6.84E-09
YBR187W	1.8	1.30E-05	YBR284W	3.5	1.50E-07
YOR073W	1.8	4.37E-06	YIL066C	3.4	1.65E-07
YJR025C	1.8	7.24E-06	YOR154W	3.4	6.67E-07
YOL069W	1.8	2.47E-05	YGR273C	3.3	1.31E-06

Table S7 continued

YCL030C	1.8	1.51E-05	YLL046C	3.3	3.45E-06
YGL187C	1.8	5.04E-06	YPR151C	3.3	1.03E-06
YPL245W	1.8	5.42E-05	YLR081W	3.2	4.05E-07
YPR191W	1.8	1.73E-05	YGL156W	3.2	4.21E-08
YBL029W	1.8	1.21E-04	YMR011W	3.1	5.45E-08
YDR503C	1.7	4.47E-05	YCL069W	3.1	5.00E-06
YBR093C	1.7	1.62E-04	YOR178C	3.0	2.28E-07
YOR164C	1.7	3.61E-06	YPL054W	3.0	4.33E-07
YMR163C	1.7	2.35E-05	YLR099C	3.0	4.29E-07
YHR051W	1.7	2.12E-05	YOR383C	3.0	1.77E-08
YIR042C	1.7	1.62E-04	YJL136W-A	3.0	1.22E-06
YDR065W	1.7	1.18E-05	YLR205C	2.9	5.10E-07
YGR020C	1.7	4.13E-05	YDR171W	2.9	1.72E-07
YHR043C	1.7	1.60E-04	YJL133C-A	2.8	1.44E-07
YBR041W	1.7	3.04E-06	YOL158C	2.8	1.57E-07
YFL003C	1.7	5.74E-05	YNL237W	2.8	7.19E-07
YBR263W	1.7	3.34E-05	YKL071W	2.8	1.58E-06
YHL018W	1.7	5.56E-04	YLR142W	2.8	7.53E-08
YHL003C	1.7	1.04E-05	YDR070C	2.8	2.72E-07
YIL029C	1.7	1.86E-03	YOR049C	2.8	5.21E-08
YML091C	1.7	2.65E-06	YMR013W-A	2.8	8.58E-06
YER078C	1.7	4.90E-05	YOL047C	2.8	7.14E-08
YHR133C	1.7	2.96E-05	YIL169C	2.8	1.52E-07

Table S7 continued

YDR321W	1.7	2.50E-06	YHL022C	2.7	1.36E-06
YEL054C	1.7	3.62E-05	YDR384C	2.7	7.82E-08
YHR015W	1.7	2.63E-05	YJL144W	2.7	6.39E-07
YBL098W	1.7	2.14E-05	YJL078C	2.7	7.54E-07
YGR165W	1.7	2.29E-05	YOR072W-B	2.7	4.52E-05
YEL052W	1.7	1.27E-05	YAR068W	2.7	9.51E-08
YMR119W	1.7	3.72E-06	YDL223C	2.7	3.73E-07
YLL005C	1.7	1.80E-02	YGR142W	2.7	2.37E-06
YLR460C	1.7	2.52E-05	YIL082W-A	2.7	1.66E-06
YPR109W	1.7	6.42E-05	YCR010C	2.6	4.28E-05
YLR038C	1.7	1.02E-04	YNR034W	2.6	2.21E-07
YBR183W	1.7	6.37E-05	YOR338W	2.6	5.60E-06
YGR117C	1.6	1.27E-05	YLR411W	2.6	4.03E-07
YOR278W	1.6	3.64E-05	YIL055C	2.6	1.38E-07
YEL001C	1.6	4.40E-05	YDR523C	2.6	1.27E-05
YNL026W	1.6	4.06E-06	YBR072C-A	2.6	4.35E-04
YLR447C	1.6	5.39E-05	YBL049W	2.6	2.88E-05
YPL208W	1.6	1.44E-04	YNL077W	2.6	1.65E-06
YGL047W	1.6	1.43E-04	YDR461W	2.5	2.03E-05
YDL198C	1.6	1.17E-05	YLR267W	2.5	1.06E-07
YKL033W-A	1.6	4.71E-05	YKL107W	2.5	3.66E-05
YOR115C	1.6	3.22E-04	YDL182W	2.5	2.05E-07
YOR071C	1.6	1.51E-05	YMR133W	2.5	6.99E-05

Table S7 continued

YDL205C	1.6	1.59E-04	YOL051W	2.5	8.87E-07
YDL116W	1.6	1.94E-05	YGR146C	2.5	2.91E-07
YLR364W	1.6	2.90E-04	YPR015C	2.5	7.06E-06
YNL130C	1.6	8.09E-05	YCR089W	2.5	1.11E-07
YPR118W	1.6	1.26E-04	YHL035C	2.5	7.69E-08
YEL064C	1.6	1.05E-05	YAR066W	2.5	5.80E-06
YHR031C	1.6	2.19E-05	YML054C	2.5	2.22E-06
YLR283W	1.6	2.33E-04	YOL155C	2.4	5.72E-08
YMR127C	1.6	1.44E-03	YER150W	2.4	7.06E-08
YDR107C	1.6	4.84E-06	YER145C	2.4	2.32E-07
YLR455W	1.6	2.04E-05	YLR194C	2.4	1.34E-06
YDR325W	1.6	2.82E-04	YHR138C	2.4	8.30E-07
YPR009W	1.6	2.95E-05	YAR071W	2.4	1.85E-06
YOL122C	1.6	1.42E-05	YBR296C	2.4	3.91E-07
YDR448W	1.6	8.23E-05	YNL075W	2.4	2.28E-07
YOR180C	1.6	4.38E-05	YEL060C	2.4	2.77E-06
YBR189W	1.6	7.57E-05	YDL173W	2.4	4.51E-07
YPR060C	1.6	1.61E-05	YGR043C	2.4	4.94E-06
YHR049W	1.6	7.19E-06	YFL014W	2.4	2.83E-06
YLR342W-A	1.6	1.70E-05	YOR237W	2.3	3.25E-06
YMR098C	1.6	3.79E-05	YBL005W	2.3	1.30E-07
YKL120W	1.6	3.18E-05	YIL099W	2.3	2.73E-05
YGL101W	1.6	8.17E-06	YKL164C	2.3	5.97E-06

Table S7 continued

YMR241W	1.6	6.62E-06	YGR109W-B	2.3	3.34E-05
YFL004W	1.6	2.40E-05	YPR124W	2.3	1.88E-06
YDL079C	1.6	2.33E-03	YPL061W	2.3	5.63E-07
YBR151W	1.6	5.74E-05	YLL042C	2.3	1.81E-05
YDR376W	1.6	3.67E-05	YMR175W	2.3	1.06E-04
YNR055C	1.6	4.49E-06	YOR302W	2.3	4.40E-05
YDL160C-A	1.6	1.11E-04	YIL056W	2.3	1.23E-06
YBL097W	1.6	4.89E-03	YAR035W	2.3	1.60E-07
YFR015C	1.6	1.15E-05	YDR270W	2.3	5.75E-07
YCR023C	1.6	2.45E-04	YOL151W	2.3	3.17E-07
YGL142C	1.6	7.21E-06	YCL044C	2.2	2.52E-06
YPR028W	1.6	2.40E-05	YGR066C	2.2	1.19E-04
YBR243C	1.6	4.94E-06	YNR044W	2.2	1.76E-06
YLR291C	1.6	1.80E-04	YGR109W-A	2.2	3.83E-05
YHR047C	1.6	5.47E-05	YPR002W	2.2	7.57E-07
YGR173W	1.6	1.42E-05	YNL212W	2.2	4.00E-07
YNR057C	1.6	2.58E-04	YKR097W	2.2	4.29E-05
YHR076W	1.6	1.09E-05	YDR246W-A	2.2	7.92E-07
YMR256C	1.6	3.90E-04	YHR143W	2.2	1.60E-06
YML096W	1.6	3.84E-05	YNL231C	2.2	2.00E-07
YIL085C	1.6	5.61E-06	YMR102C	2.2	3.33E-07
YPR119W	1.6	2.49E-05	YKL163W	2.2	9.35E-06
YGL155W	1.6	1.29E-04	YLR070C	2.2	8.35E-06

Table S7 continued

YGR004W	1.6	8.52E-06	YBR047W	2.2	3.88E-06
YKL134C	1.6	6.71E-06	YBR066C	2.2	8.58E-07
YOR239W	1.6	9.96E-06	YNL037C	2.2	1.01E-06
YBR048W	1.6	1.76E-04	YOR152C	2.2	1.66E-07
YIL009C-A	1.6	1.91E-05	YMR058W	2.2	1.50E-07
YNL168C	1.6	6.12E-06	YJR091C	2.2	3.69E-06
YKL183W	1.6	6.61E-05	YBR071W	2.1	1.47E-05
YDR046C	1.6	5.80E-06	YPL247C	2.1	3.14E-07
YJR015W	1.6	9.58E-06	YPR184W	2.1	4.83E-07
YHL015W	1.6	2.99E-05	YPR108W-A	2.1	1.21E-04
YNR059W	1.6	1.28E-04	YIL134C-A	2.1	5.94E-05
YER141W	1.6	7.42E-06	YMR181C	2.1	5.80E-06
YNL069C	1.6	1.12E-05	YFR032C	2.1	3.04E-06
YHR032W	1.6	4.60E-05	YGR146C-A	2.1	2.12E-05
YER157W	1.6	1.63E-04	YBR117C	2.1	2.75E-06
YMR126C	1.6	1.45E-04	YOL010W	2.1	1.03E-06
YPL122C	1.6	9.22E-06	YER002W	2.1	6.32E-07
YLR143W	1.6	2.14E-05	YNL251C	2.1	2.26E-06
YEL050C	1.6	1.66E-05	YBR298C-A	2.1	3.13E-04
YML106W	1.6	9.13E-06	YPL017C	2.1	2.15E-06
YKR062W	1.6	1.30E-05	YBR212W	2.1	1.05E-05
YPL148C	1.6	3.88E-05	YNL194C	2.1	1.39E-06
YFR005C	1.6	2.05E-04	YER028C	2.1	9.75E-06

Table S7 continued

YDR245W	1.6	9.90E-06	YGR023W	2.1	3.09E-05
YNR003C	1.6	2.74E-04	YHR086W-A	2.1	1.08E-04
YOR317W	1.6	1.09E-05	YAL012W	2.1	4.78E-07
YDR235W	1.6	3.86E-04	YPL111W	2.1	2.78E-06
YBR074W	1.5	1.24E-05	YOR183W	2.1	1.57E-03
YNL010W	1.5	2.27E-04	YJR150C	2.1	5.67E-05
YOR184W	1.5	1.58E-04	YOR303W	2.0	4.09E-07
YDR372C	1.5	1.60E-05	YPL201C	2.0	6.37E-04
YLR022C	1.5	5.00E-05	YPL171C	2.0	8.31E-06
YMR299C	1.5	2.21E-04	YLR327C	2.0	3.09E-06
YML067C	1.5	5.16E-05	YER037W	2.0	1.42E-06
YGR208W	1.5	6.30E-06	YML083C	2.0	3.27E-05
YDL080C	1.5	4.92E-05	YPR065W	2.0	7.22E-05
YMR230W	1.5	5.94E-04	YOR153W	2.0	9.56E-07
YDR089W	1.5	1.08E-05	YHR179W	2.0	4.31E-07
YFR009W	1.5	2.92E-05	YMR182C	2.0	3.52E-05
YGL191W	1.5	3.83E-04	YOL152W	2.0	6.26E-05
YML108W	1.5	1.20E-03	YOR023C	2.0	1.83E-06
YDR364C	1.5	6.93E-05	YDR258C	2.0	1.76E-06
YOR038C	1.5	1.56E-05	YNL036W	2.0	2.88E-05
YHR001W-A	1.5	1.58E-04	YPL230W	2.0	1.76E-05
YOL076W	1.5	4.39E-03	YOL022C	2.0	1.54E-06
YOL064C	1.5	2.97E-05	YDR256C	2.0	4.24E-05

Table S7 continued

YER060W	1.5	4.90E-05	YGR249W	2.0	5.39E-06
YIL016W	1.5	7.95E-06	YER103W	2.0	8.45E-07
YJR054W	1.5	2.47E-05	YIL135C	2.0	3.56E-05
YGR216C	1.5	5.20E-05	YJL049W	2.0	6.45E-06
YBR021W	1.5	1.34E-04	YJL089W	2.0	5.53E-06
YCR107W	1.5	1.24E-02	YOR374W	2.0	3.32E-06
YJL051W	1.5	2.40E-05	YDL114W	2.0	5.64E-04
YDR118W	1.5	1.16E-04	YDL222C	2.0	3.49E-05
YOR241W	1.5	1.46E-05	YAL062W	2.0	9.28E-06
YDR370C	1.5	1.37E-04	YGL244W	2.0	1.69E-06
YJR143C	1.5	1.38E-05	YLR040C	2.0	2.32E-06
YHR113W	1.5	2.76E-05	YOL036W	2.0	2.90E-06
YPR056W	1.5	1.40E-03	YDL169C	1.9	3.58E-06
YIL014W	1.5	2.73E-05	YDR453C	1.9	1.10E-06
YLR363C	1.5	3.27E-05	YBR006W	1.9	5.53E-07
YGL159W	1.5	3.48E-04	YGL121C	1.9	5.38E-05
YJL181W	1.5	2.48E-05	YBR018C	1.9	2.03E-05
YDL069C	1.5	5.61E-04	YEL070W	1.9	1.07E-05
YCR043C	1.5	4.42E-05	YBL078C	1.9	1.58E-06
YDL066W	1.5	1.64E-04	YBR238C	1.9	3.67E-05
YGR033C	1.5	2.35E-05	YOR316C	1.9	2.04E-06
YPL227C	1.5	1.75E-05	YNL195C	1.9	1.95E-05
YLL041C	1.5	6.26E-05	YER169W	1.9	3.76E-06

Table S7 continued

YMR035W	1.5	1.68E-03	YNL277W-A	1.9	5.14E-06
YJL072C	1.5	1.33E-04	YKR092C	1.9	1.31E-05
YJL166W	1.5	6.72E-05	YNL095C	1.9	6.57E-06
YBR297W	1.5	4.64E-05	YNL160W	1.9	3.59E-05
YMR210W	1.5	1.50E-05	YBR072W	1.9	2.47E-06
YPL083C	1.5	1.79E-05	YHR027C	1.9	6.96E-07
YMR117C	1.5	1.94E-03	YJR095W	1.9	2.95E-04
YBR129C	1.5	1.41E-03	YCL039W	1.9	1.12E-06
YGR222W	1.5	5.52E-05	YDR195W	1.9	5.35E-07
YLR351C	1.5	5.62E-05	YHR176W	1.9	8.09E-05
YBR219C	1.5	6.56E-05	YGR144W	1.9	3.23E-05
			YCR061W	1.9	1.98E-05
			YJL125C	1.9	1.52E-06
			YER011W	1.9	1.30E-05
			YOR192C-C	1.9	1.65E-05
			YIL155C	1.9	4.00E-06
			YBR301W	1.9	3.00E-05
			YMR108W	1.9	3.64E-05
			YGL209W	1.9	6.32E-07
			YGL179C	1.9	1.40E-05
			YBR085C-A	1.9	1.48E-05
			YGL073W	1.8	3.01E-06
			YPL223C	1.8	9.68E-06

Table S7 continued

			YNL146C-A	1.8	8.34E-06
			YKR011C	1.8	1.80E-06
			YMR309C	1.8	3.03E-06
			YKR039W	1.8	1.72E-06
			YLR149C	1.8	7.11E-07
			YOR173W	1.8	1.22E-05
			YJL026W	1.8	9.09E-06
			YER104W	1.8	5.15E-04
			YHR081W	1.8	2.28E-06
			YGR110W	1.8	6.85E-05
			YLR031W	1.8	4.67E-04
			YHR126C	1.8	2.64E-04
			YKR076W	1.8	6.26E-06
			YDR194W-A	1.8	6.00E-04
			YPL159C	1.8	2.45E-06
			YJL170C	1.8	6.53E-04
			YLR030W	1.8	6.23E-04
			YLR214W	1.8	1.21E-05
			YPR030W	1.8	4.22E-06
			YMR069W	1.8	9.10E-05
			YGR243W	1.8	3.60E-05
			YHR177W	1.8	3.67E-04
			YMR101C	1.8	2.22E-05

Table S7 continued

			YKR077W	1.8	8.28E-05
			YHR124W	1.8	1.10E-04
			YPR040W	1.8	1.02E-05
			YJR115W	1.8	1.34E-06
			YDR403W	1.8	1.72E-05
			YOR287C	1.8	1.83E-05
			YBL101W-A	1.8	1.31E-04
			YNL277W	1.8	4.25E-05
			YOL119C	1.8	2.14E-06
			YBR214W	1.8	1.02E-04
			YBL108C-A	1.8	1.27E-04
			YCR021C	1.8	7.75E-05
			YGL228W	1.8	4.18E-06
			YBL051C	1.8	3.87E-05
			YFL016C	1.8	2.31E-06
			YLL023C	1.8	3.27E-06
			YNL074C	1.7	1.28E-05
			YPL088W	1.7	1.86E-04
			YIL136W	1.7	5.92E-06
			YBR208C	1.7	3.22E-06
			YDL054C	1.7	1.77E-05
			YOR344C	1.7	2.66E-05
			YGR239C	1.7	1.13E-05

Table S7 continued

			YPL027W	1.7	1.09E-03
			YBR016W	1.7	5.11E-06
			YAL002W	1.7	4.52E-06
			YBR067C	1.7	4.82E-06
			YNL014W	1.7	2.22E-06
			YDL020C	1.7	1.58E-05
			YLR056W	1.7	3.90E-05
			YIL176C	1.7	6.84E-05
			YGL051W	1.7	4.78E-03
			YNL327W	1.7	9.26E-06
			YJL050W	1.7	7.39E-06
			YOR252W	1.7	1.05E-04
			YLR213C	1.7	2.84E-06
			YLL052C	1.7	7.66E-05
			YML128C	1.7	1.79E-05
			YGL071W	1.7	6.22E-06
			YIL046W-A	1.7	2.74E-04
			YDR312W	1.7	4.07E-05
			YDL038C	1.7	1.10E-04
			YGR256W	1.7	7.38E-06
			YNR067C	1.7	7.61E-06
			YPL051W	1.7	1.98E-05
			YGR213C	1.7	5.93E-04

Table S7 continued

			YOR208W	1.7	5.50E-06
			YCR077C	1.7	3.47E-06
			YOL123W	1.7	1.02E-05
			YMR041C	1.7	6.51E-06
			YDL085W	1.7	1.58E-04
			YDL161W	1.7	3.20E-05
			YBL054W	1.7	7.74E-06
			YBL005W-A	1.7	9.50E-04
			YHR048W	1.7	3.15E-04
			YDR516C	1.7	2.21E-05
			YDR253C	1.7	8.60E-04
			YPR036W-A	1.7	4.57E-06
			YDR476C	1.7	1.98E-04
			YMR043W	1.7	6.09E-05
			YGR201C	1.7	2.19E-05
			YKL029C	1.7	1.15E-05
			YJR151C	1.7	1.10E-05
			YMR294W	1.7	1.10E-05
			YFL021W	1.7	1.85E-05
			YOL058W	1.7	4.57E-05
			YBR207W	1.7	8.03E-06
			YPL068C	1.7	6.68E-06
			YML034W	1.7	8.87E-06

Table S7 continued

			YMR196W	1.7	3.82E-06
			YPL089C	1.7	1.58E-04
			YLL026W	1.7	1.51E-05
			YPL222W	1.7	8.84E-06
			YNL208W	1.6	1.26E-05
			YMR016C	1.6	2.41E-05
			YJL149W	1.6	9.17E-06
			YAL068C	1.6	9.22E-04
			YJL037W	1.6	1.15E-04
			YMR291W	1.6	2.46E-05
			YLR370C	1.6	3.58E-05
			YDL215C	1.6	1.10E-05
			YPL252C	1.6	5.34E-06
			YIL117C	1.6	5.51E-06
			YLL053C	1.6	2.08E-05
			YKR049C	1.6	4.89E-05
			YLR461W	1.6	2.04E-05
			YML015C	1.6	5.86E-06
			YMR322C	1.6	9.71E-05
			YLL064C	1.6	3.08E-05
			YER045C	1.6	9.57E-06
			YKL032C	1.6	1.88E-04
			YFR017C	1.6	2.77E-05

Table S7 continued

			YOR328W	1.6	1.74E-04
			YBR147W	1.6	6.39E-05
			YJL079C	1.6	1.86E-04
			YPL135W	1.6	6.44E-06
			YGR060W	1.6	7.63E-06
			YOL084W	1.6	1.72E-04
			YJL033W	1.6	6.52E-05
			YGR019W	1.6	3.26E-05
			YBR105C	1.6	1.04E-04
			YIL013C	1.6	1.83E-04
			YKL112W	1.6	3.59E-05
			YBL046W	1.6	4.44E-06
			YLR094C	1.6	2.73E-05
			YGL192W	1.6	4.53E-03
			YKL106C-A	1.6	1.79E-03
			YGL180W	1.6	1.47E-04
			YJL082W	1.6	1.76E-05
			YLR079W	1.6	5.65E-05
			YPL156C	1.6	8.17E-06
			YBR108W	1.6	2.50E-04
			YPL265W	1.6	2.01E-05
			YNL076W	1.6	9.28E-06
			YLR312C	1.6	1.15E-05

Table S7 continued

			YOR289W	1.6	1.80E-05
			YOL059W	1.6	1.77E-04
			YDR177W	1.6	2.78E-05
			YGR087C	1.6	1.23E-03
			YPR159C-A	1.6	4.00E-03
			YNL042W-B	1.6	9.73E-05
			YLL039C	1.6	5.54E-05
			YMR034C	1.6	2.72E-05
			YDR309C	1.6	4.76E-05
			YML130C	1.6	2.74E-05
			YOR227W	1.6	1.41E-05
			YPL229W	1.6	4.11E-04
			YEL012W	1.6	3.10E-05
			YEL069C	1.6	2.40E-02
			YGR212W	1.6	9.36E-05
			YHR148W	1.6	2.19E-04
			YNL216W	1.6	4.08E-05
			YDL204W	1.6	3.54E-04
			YAL025C	1.6	1.46E-05
			YGL178W	1.6	2.34E-04
			YDR172W	1.6	2.47E-05
			YJL159W	1.6	8.67E-06
			YGL028C	1.6	1.94E-05

Table S7 continued

			YBR285W	1.6	2.11E-04
			YOR009W	1.6	1.43E-03
			YGL021W	1.6	9.47E-06
			YER179W	1.6	1.83E-04
			YPL093W	1.6	8.06E-06
			YDR120C	1.6	2.63E-05
			YDL024C	1.6	4.63E-05
			YOR100C	1.6	1.05E-04
			YLR285C-A	1.6	1.10E-05
			YNR075W	1.6	5.07E-05
			YER096W	1.6	6.93E-04
			YKL221W	1.6	5.81E-04
			YML092C	1.6	7.26E-06
			YIL070C	1.6	2.23E-05
			YBR029C	1.6	7.48E-05
			YLR377C	1.6	1.06E-02
			YER100W	1.6	3.30E-04
			YLR154C-H	1.6	6.11E-04
			YGL215W	1.6	5.16E-04
			YER185W	1.6	5.38E-06
			YGR041W	1.6	1.69E-05
			YOL071W	1.6	9.27E-05
			YGL023C	1.6	9.23E-06

Table S7 continued

			YHR052W	1.6	1.36E-05
			YDL093W	1.6	1.54E-05
			YPR112C	1.6	2.00E-05
			YKL070W	1.6	3.54E-03
			YOR214C	1.6	2.35E-02
			YOR294W	1.6	9.09E-06
			YDL178W	1.6	2.14E-04
			YLR286C	1.6	8.21E-06
			YMR140W	1.6	9.51E-05
			YBL043W	1.6	3.52E-03
			YDR358W	1.6	1.92E-04
			YHR205W	1.5	5.30E-05
			YDR218C	1.5	1.30E-03
			YAL055W	1.5	8.56E-05
			YLR042C	1.5	2.23E-04
			YOR394W	1.5	2.88E-04
			YGR058W	1.5	2.31E-04
			YIL011W	1.5	3.68E-04
			YFR034C	1.5	2.07E-04
			YNR015W	1.5	7.59E-06
			YOL054W	1.5	2.34E-05
			YDL123W	1.5	2.66E-04
			YAL034C	1.5	5.22E-05

Table S7 continued

			YPR094W	1.5	1.03E-04
			YIL107C	1.5	6.69E-06
			YLR390W-A	1.5	1.46E-04
			YDR011W	1.5	1.65E-04
			YDR055W	1.5	8.39E-04
			YDL124W	1.5	8.00E-05
			YGR131W	1.5	5.21E-05
			YML007W	1.5	2.05E-04
			YBR135W	1.5	8.07E-05
			YER158C	1.5	1.20E-04
			YOR306C	1.5	2.53E-04
			YDR492W	1.5	6.47E-05
			YDL130W-A	1.5	6.50E-04
			YMR031C	1.5	3.84E-05
			YER069W	1.5	1.16E-05
			YOR054C	1.5	4.06E-05
			YMR206W	1.5	1.23E-03
			YCR053W	1.5	3.10E-05
			YNL027W	1.5	1.40E-05
			YER079W	1.5	5.49E-05
			YJL088W	1.5	1.76E-05
			YEL047C	1.5	3.04E-05
			YNL308C	1.5	3.69E-05

Table S7 continued

			YDR402C	1.5	3.32E-04
			YOL162W	1.5	1.83E-03
			YAL039C	1.5	2.46E-05
			YPL033C	1.5	2.68E-03
			YGR189C	1.5	8.82E-04
			YOR267C	1.5	8.72E-05
			YGR082W	1.5	3.94E-05
			YFL041W	1.5	2.08E-05
			YJR094C	1.5	2.22E-04
			YFL001W	1.5	2.98E-05
			YIR025W	1.5	1.85E-05
			YLR156W	1.5	8.50E-04
			YGR005C	1.5	1.15E-04
			YNR014W	1.5	1.78E-03
			YKL084W	1.5	1.48E-05
			YLR254C	1.5	5.36E-05

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EDUCATION

2011 - Present Ph.D. Bioengineering - Marmara University, Institute of Graduate Studies in Pure and Applied Sciences, Istanbul, Turkey

"Investigation of the effects of endocrine disrupting compounds on the transcriptional profile of *Saccharomyces cerevisiae*"

2008 - 2010 M.S. Medical Biology and Genetics – Cukurova University, Institute of Medical Sciences, Adana, Turkey

"Studies on *interleukin 10* gene promoter (2849 A-G) and angiotensin converting enzyme intron 16 insertion/deletion polymorphisms and genotype distributions in preeclampsia patients"

2001 - 2006 B.S. Molecular Biology and Genetics – Istanbul Technical University, Science and Letter Faculty, Department of Molecular Biology and Genetics, Istanbul, Turkey

ACADEMIC EXPERIENCE

Research Assistant Marmara University, Institute of Graduate Studies in Pure and Applied Sciences, Department of Bioengineering, Istanbul, Turkey (**2011-Present**)

FIELDS OF EXPERIENCES & INTERESTS

Molecular biology and genetics, microbial ecotoxicology, biological networks, systems biology, yeast genetics.

Molecular techniques (polymerase chain reaction (PCR), real-time PCR, fluorescent in-situ hybridization (FISH), restriction fragment length polymorphism (RFLP), DNA sequencing).

COURSES & LABORATORIES TAUGHT

General Biology Laboratory
Microbiology Laboratory
Biochemistry Laboratory
Molecular Biology and Genetics Laboratory
Medical Biology and Genetics Laboratory

PUBLICATIONS

Journal Papers (SCI Index)

1. Ucar D., Cokgor E.U., Sahinkaya E., Cetin U., **Bereketoglu C**., Calimlioglu B., Goncu B., Yurtsever A. **(2017)**. Simultaneous nitrate and perchlorate removal from groundwater by heterotrophic-autotrophic sequential system. *Int Biodeterior Biodegradation*. 116; 83-90.

2. Bereketoglu C., Arga K.Y., Eraslan S., Mertoglu B. **(2016)**. Analysis of transcriptional profiles of *Saccharomyces cerevisiae* exposed to bisphenol A. *Curr Genet.* doi:10.1007/s00294-016-0633-z.

3. Pazarbasi A., Yilmaz M.B., Alptekin D., Luleyap U., Tansug Z., Ozpak L., Izmirli M., Onatoglu-Arikan D., Kocaturk-Sel S., Erkoc M.A., Turgut O., **Bereketoglu C.**, Tunc E., Akbal E. **(2013)**. Genetic polymorphisms of estrogen receptor alpha and catethol-O-methyltransferase genes in Turkish patients with familial prostate carcinoma. *Indian J Hum Genet*, 19 (4); 408-411.

4. Bereketoğlu C., Kasap M., and Pazarbaşı A. (**2012**). Studies on angiotensin-converting enzyme insertion/deletion polymorphism and genotype distributions in Turkish preeclampsia patients. *Journal of Pregnancy*, vol. 2012, Article ID 108206, 4 pages, doi:10.1155/2012/108206.

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1. Erkoç M.A., **Bereketoğlu C**., Alptekin D. (**2010**). Genetic risk factors in chronic obstructive lung disease (COPD). *Archives Medical Review Journal*, 19 (3); 168-179. Turkish.

Conference and Course Proceedings

1. Bereketoglu C., Arga K.Y., Mertoglu B. **(2016)**. "Investigating the toxic effects of nonylphenol on Saccharomyces cerevisiae" 17th European Congress on Biotechnology, July 3-6, Krakow, Poland. **(Poster Presentation)**

2. Bereketoglu C., Arga K.Y., Eraslan S., Mertoglu B. **(2016)**. "Transcriptional analysis of nonylphenol on Saccharomyces cerevisiae using DNA microarray" Gene transcription in yeast: From chromatin to RNA and back, June 11-16, Sant Feliu de Guixols, Spain. **(Poster Presentation)**

3. Bereketoglu C., Arga K.Y., Mertoglu B. **(2014)**. "Research on the action mechanisms of endocrine disrupting chemicals via systems biology approach" *Advance Lecture Course on Systems Biology "SysBio2014"*, March 2-8, Innsbruck, Austria. **(Poster Presentation)**

4. Bereketoglu C. (**2013**). "Investigating the effects of endocrine disrupting chemicals from yeast systems biology perspective" *6th International Course in Yeast Systems Biology*, June 3-10, University of Gothenburg, Sweden. **(Oral Presentation)**

5. Bereketoğlu C., Kasap M., Pazarbaşı A., Özgünen F.T., Bağış T., Yılmaz M. B., Erkoç M.A. (**2011**). "Studies on interleukin 10 gene -2849 promoter and angiotensin converting enzyme insertion/deletion polymorphisms in Turkish preeclampsia patients" *4th International Congress of Molecular Medicine*, June 27-30, Istanbul, Turkey. **(Poster Presentation)**

Conference and Course Proceedings (Turkish)

1. Erkoç M.A., Alptekin D., Yılmaz B., **Bereketoğlu C**., Kocatürk Sel S. (**2011**) "TNF alpha G-308A, TGF beta C-509T and T869C polymorphisms in chronic obstructive lung disease (COPD) patients" *12th National Congress of Medical Biology and Genetics*, October 27-30, Antalya, Turkey. **(Poster Presentation)**

2. Tanrıverdi N., Karahan Süleymanova D., Taşdemir D., Güney İ., Karakan Z., **Bereketoğlu C**., Tunç E., Demirhan O. (**2009**) "Existence of translocation between both spouses [T(16;19)(Q24;12)X2] of non-homologous two chromosomes in a patient with atypical facial appearance and mental retardation" *11th National Congress of Medical Biology and Genetics*, October 28-31, Bodrum, Turkey. **(Poster Presentation)**