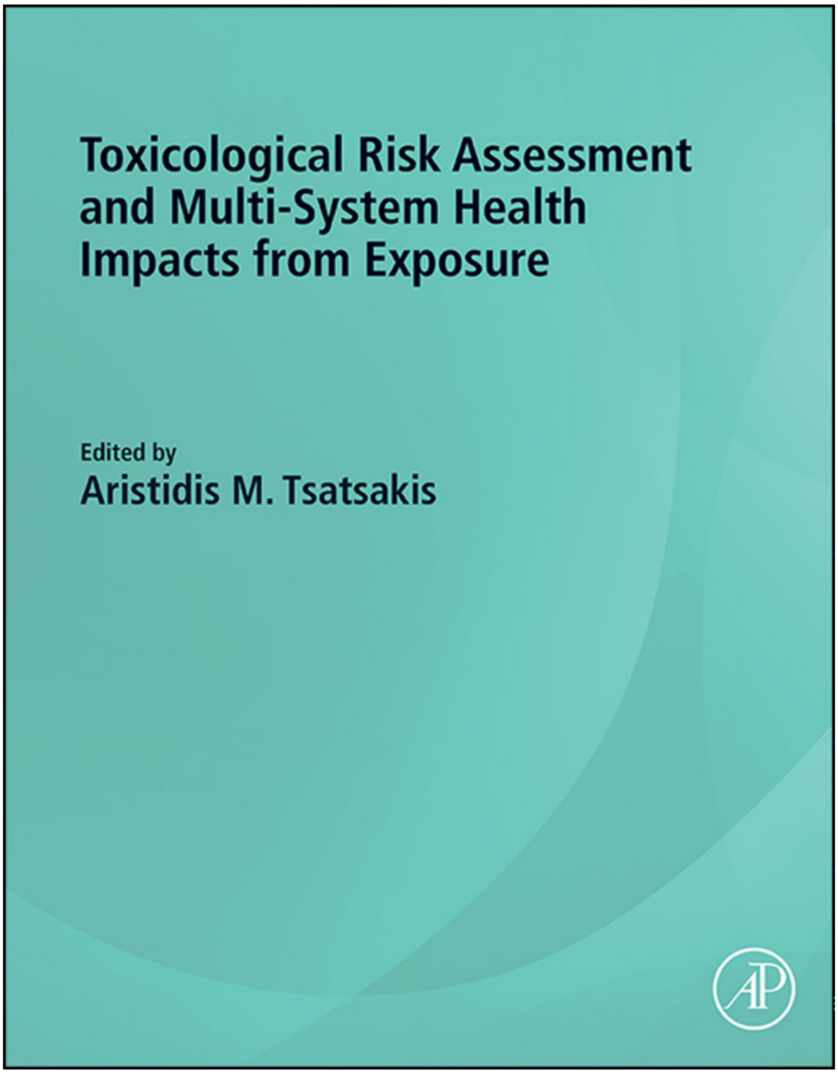

From Aristidis S. Veskoukis, Redox biomarkers in toxicology and nutrition: the social link. In: Aristidis M. Tsatsakis, editors, Toxicological Risk Assessment and Multi-System Health Impacts from Exposure. Chennai: Academic Press, 2021, pp. 427-434.
ISBN: 978-0-323-85215-9

Academic Press.

Chapter 36

Redox biomarkers in toxicology and nutrition: the social link

Aristidis S. Veskoukis

Department of Nutrition and Dietetics, School of Physical Education, Sport Science and Dietetics, University of Thessaly, Trikala, Greece

36.1 Introduction

Toxicology is a fundamental scientific area whose basic ideas originate back to the 5th century BCE (Sykiotis et al., 2005). At that time, Hippocrates, who has been characterized as *the father of modern Medicine*, introduced experiment as a practice of medicine keeping science away from the superstitions dominating during his era. Furthermore, he perceived the principle of pharmacogenetics according to which the efficiency or the potential harmful effects of drugs (i.e., xenobiotics as we know today) are highly dependent on the genetic background of the recipient (Sykiotis et al., 2005). During the 16th century CE, Paracelsus who is considered *the father of toxicology,* was the first to express the notion that *the dose makes the poison* paving actually the way for the NOAEL (no-observed-adverse-effect level) on xenobiotic administration (Tsatsakis et al., 2018).

On the basis of this idea, a new concept has emerged during the last 5 years, named as the *real-life exposure scenario* or *the real-life risk simulation* (RLRS) (Tsatsakis et al., 2016, 2017). This is a novel approach according to which, humans get in contact during their everyday life with mixtures of xenobiotics in small concentrations that are seemingly harmless. Nevertheless, the effects of xenobiotic mixtures administered long term in small concentrations (far below NOAEL) have not yet been elucidated. A limited number of studies so far have tried to shed light on this issue indicating that the long-term low-dose regimen of xenobiotic administration on experimental animals exerts detrimental action on several health parameters (Docea et al., 2016, 2018, 2019; Fountoucidou et al., 2019). In these terms, a perception shift, as previously defined, has been formulated in the ideas in the field of toxicology (Veskoukis, 2020) (Fig. 36.1). This pioneering toxicological conception integrates toxicology with two other research disciplines, namely redox biology and nutrition. On the one hand, the effects of the long-term low-dose administration regimen of xenobiotics exerts noteworthy effects on blood and tissue redox homeostasis and equilibrium, which are evaluated through the measurement of specific redox biomarkers (Veskoukis et al., 2019; Fountoucidou et al., 2019; Docea et al., 2018). On the other hand, a concrete association between toxicology and nutrition has been established. Indeed, since 1990 it has been stated that there are three basic elements in the field of nutritional toxicology as follows: the influence of nutrition and diet on the response of an organism on xenobiotic administration, the effects of xenobiotics on the nutritional requirements and the function of nutritive substances and, finally, the toxic action of nutrients when they are consumed in excessively high doses (Hathcock, 1990). This chapter will further delve into the decisive role of nutrition on the outcome of xenobiotic administration on several health and well-being parameters and, especially, redox status by examining *the biomarker issue*, as it has been previously defined (Veskoukis et al., 2019).

36.2 The biomarker issue in a wide range of scientific disciplines

The *biomarker issue* has been introduced as *the rationale of adopting biomarkers in order to address scientific queries* (Veskoukis et al., 2019). It appears that the use of biomarkers is a valuable tool in order to approach questions in diverse research areas. In medicine, several parameters measured in blood are related to pathologies. For example, the elevated transaminases, commonly alanine transaminase and aspartate transaminase, are indices of liver damage (Giboney, 2005). In exercise biochemistry, lactic acid levels in blood are increased after strenuous exercise followed by a burning feeling in the muscular system and probably impairs exercise performance (Cairns, 2006). In the field of

Toxicological Risk Assessment and Multi-System Health Impacts from Exposure. DOI: https://doi.org/10.1016/B978-0-323-85215-9.00038-6

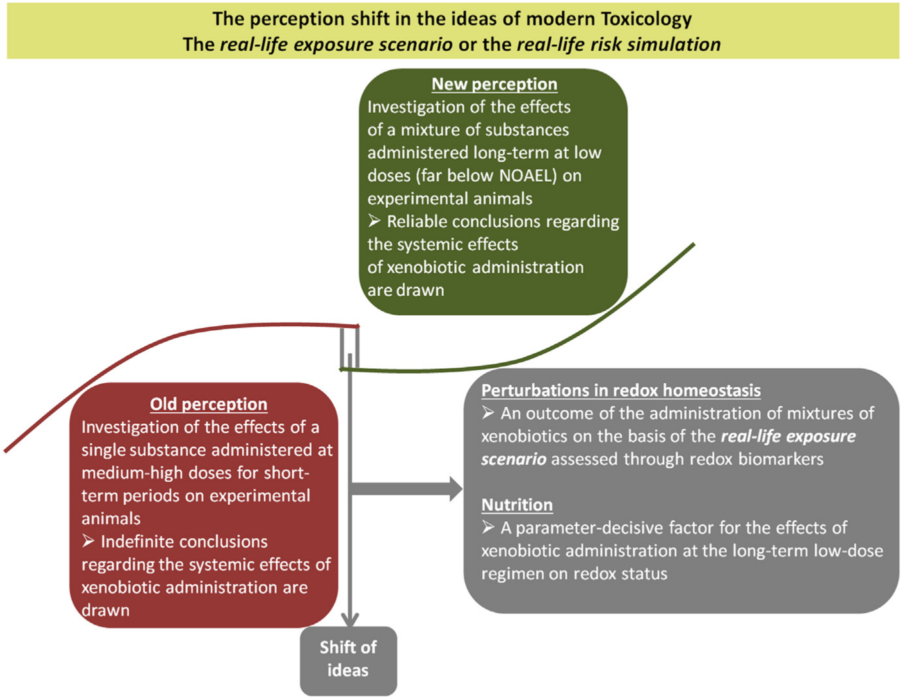

FIGURE 36.1 The perception shift in the ideas of modern toxicology. Integration of the research fields of redox biology, through the adoption of redox biomarkers for the evaluation of perturbations in redox homeostasis, and nutrition, since diet is a decisive factor for assessing the effects of xenobiotic administration on the basis of the *real-life exposure scenario* or, alternatively, the *real-life risk simulation* concept emerged at the research area of toxicology.

nutrition, elevated concentration of carotenoids and vitamin C have been related to adequate consumption of fruit and vegetables through diet (Picó et al., 2019).

The term biomarker has been defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention, by the Biomarkers Definitions Working Group (2001). In the field of toxicology, there are two influential definitions of biomarker. One of them has been given by the National Academy of Sciences (ENTOX/TIWET, 1996) and proposes that a biomarker is a xenobiotically induced alteration in cellular or biochemical components or processes, structures, or functions that is measurable in a biological system or sample and the other is as follows: a physiological signal that reflects exposure, early cellular response, or inherent or acquired susceptibilities, which provide a new strategy for resolving some toxicological problems (Silbergeld and Davis, 1994). To this end, skeletal troponin T and myosin light chain 3 are promising biomarkers that indicate muscle toxicity (Campion et al., 2013). Recent studies, however, have revealed that, since xenobiotics induce perturbations in redox equilibrium, redox biomarkers seem to be reliable indices for monitoring toxicity in blood and tissues (Docea et al., 2018; Fountoucidou et al., 2019). The definition of the term redox biomarker has been given very recently as follows: a biological entity that can be accurately and reproducibly measured and that might be: (1) an antioxidant molecule (e.g., glutathione, catalase), whose concentration, activity, and/or structure are modified following interaction with reactive species (RS); (2) the products of the detrimental impact of RS on biomolecules (e.g., protein carbonyls, malonyldialdehyde); and (3) the RS *per se* (Veskoukis et al., 2019). It has to be mentioned that tens of redox biomarkers have been recognized. Hence, it is a hard task to pick the appropriate ones in order to end up with solid conclusions. It has, therefore, been proposed that the selected redox biomarkers to be measured should be functionally and structurally clustered forming networks with translational potency (Veskoukis et al., 2016a, 2018a,b, 2019). Two other key parameters that are inextricably linked to alterations in redox status due to xenobiotics are nutrition and diet. It becomes evident that several traits of nutrient consumption such as the concentration, the frequency, and the genetic background of the recipient are fundamental in order to predict the role of nutrition as a sociomarker (Ghezzi, 2020) on the redox status after administration of toxic substances. This is an idea that will be expanded on later on in this chapter.

36.3 The role of redox biomarkers in the interpretation of perturbations in redox equilibrium

Redox equilibrium in cell culture models (i.e., *in vitro*) and *in vivo* (i.e., experimental animals and humans) is normally modified after implication of redox-altering stimuli (Veskoukis et al., 2019). Some very common treatments with this characteristic are antioxidant administration (i.e., nutritional interventions); exercise; administration of xenobiotics (the following section will focus on such studies); and numerous pathologies. The available literature indicates that it is not clear whether the aforementioned stimuli change redox homeostasis toward a specific direction at the redox continuum, meaning that it is difficult to characterize any given treatment as antioxidant or prooxidant (Veskoukis et al., 2020). This fact can be insightfully characterized as the *Rashomon effect* (Nikolaidis and Margaritelis, 2018). Although the administration of an antioxidant could easily be considered a beneficial treatment, experimental findings have revealed a Janus-faced action of antioxidant substances, which can either be harmless or even detrimental, especially in exercise context (Margaritelis et al., 2018). In this line of evidence, antioxidants are necessary in order for any individual to obtain useful adaptations but they may also act as foe (Veskoukis et al., 2008, 2009, 2010, 2012a, 2016b; Kerasioti et al., 2012). Therefore the personalized regimen for antioxidant administration has emerged during the last few years. This is an approach based on the idea that an antioxidant is beneficial if the baseline values of endogenous blood antioxidants of the recipient are low, meaning that the possibilities to be beneficial are high due to the increased need of an organism for this compound (Margaritelis et al., 2018; Spanidis et al., 2018). This concept also applies to studies that examine the amelioration of the symptoms of several diseases after antioxidant supplementation, however, it is even harder to foresee the way of action of a compound with either plant or animal origin (Veskoukis et al., 2012a,b, 2020; Kerasioti et al., 2019; Kouka et al., 2020).

Concerning the impact of antioxidants on redox-related diseases, it appears that it is rather complicated to reveal it. Indeed, taking cancer as an example, although it was believed until recently that antioxidants could serve as therapeutic factors, it has lately been demonstrated that RS are detrimental for cancer cells and therefore antioxidants largely contribute to cancer progression and metastasis (Le Gal et al., 2015). This and other similar experimental evidence clearly show that RS do not exert clinical significance, according to the current knowledge (Veskoukis et al., 2020). In particular, it is not yet known whether specific RS possess a cause-effect relation to redox-related diseases (e.g., cardiovascular, cancer, diabetes) (Ghezzi et al., 2020; Veskoukis et al., 2020). This is an essential issue in the field of redox biology since it partly explains the dual role of antioxidants as putative therapeutic factors. The use of redox biomarkers is a valuable tool in order to evaluate the effects of antioxidants on disease, as was stated in the previous paragraphs.

36.4 Redox biomarkers in toxicology and nutrition

It is established that toxicological and nutritional interventions, apart from their potential impact on health-related parameters and pathology onset, are able to alter redox equilibrium throughout the redox continuum. Administration of xenobiotics and antioxidants usually modifies redox homeostasis either by generating useful adaptations or by inducing disruptions in redox signaling, thus oxidative stress (Jones, 2006; Veskoukis et al., 2012b; Docea et al., 2018; Fountoucidou et al., 2019). Such alterations are usually monitored through the measurement of networks of redox biomarkers (Veskoukis et al., 2016a, 2018a). Several studies have examined the effects of xenobiotic administration on oxidative stress and they have largely correlated xenobiotic toxicity with impaired antioxidant defense and oxidative modifications of macromolecules (Deavall et al., 2012; Docea et al., 2018; Fountoucidou et al., 2019). However, short-term administration of mixtures of xenobiotics in concentrations far below NOAEL produces useful adaptations allowing the organism to overcome the detrimental action due to their bioaccumulation in blood and tissues, a finding that is inverted after long-term administration (Docea et al., 2018; Fountoucidou et al., 2019). Similarly, the effects of nutritional supplements or plant- and animal-derived antioxidants seem to be twofold, due to parameters analyzed in the previous paragraphs (Veskoukis et al., 2012a; Draganidis et al., 2016; Kourtzidis et al., 2018). It can be deduced, hence, that irrespective of the outcome of toxicological or nutritional interventions, redox biomarkers are appropriate indices in order to depict alterations in redox status that are associated with pathological conditions (Veskoukis et al., 2020).

36.5 Nutrition, toxicology, and redox biology: an interplay

The role of xenobiotic administration as a redox-altering stimulus (i.e., able to change and even disrupt redox homeostasis monitored by measuring redox biomarkers) and as a treatment that induces toxicity and several related pathologies has been examined in the previous sections of this chapter. The ability of nutrition to induce alterations on redox status *in vivo* assessed by measuring redox biomarkers has also been discussed. However, in terms of interplay between the research areas of nutrition, toxicology, and redox biology, nutrition and diet are key factors for assessing the impact of toxicological treatments on blood and tissue redox status.

36.5.1 Nutrition, a sociomarker

Nutrition, a fundamental parameter of human existence, is considered a sociomarker (Ghezzi, 2020). Therefore we will make an effort to introduce the concept of sociomarkers in parallel with biological markers (i.e., biomarkers) and to associate it with the health impairment and the disease onset keeping toxicity assessment in the spotlight. Nutrition and toxicity of xenobiotics are basic factors that putatively influence detrimentally human health. Health is a commodity with both a biological and a social nature. Indeed, disease is the biological branch formulated in our case by the toxic action of xenobiotics and factors such as nutrition constitute the social side of health. Although it seems to be rather clear how xenobiotic administration affects health, the case for nutrition is not. Interestingly, malnutrition or poor nutrition, probably due to other social factors, namely poverty and social exclusion, definitely acts negatively on health, but this is not the case for nutritional antioxidants. We have to keep in mind that it is difficult to guess whether specific antioxidants are anticipated to exert positive or negative effects unless parameters like the biological role and the concentration of the administered antioxidant or the genetic background and the baseline values of some crucial antioxidants (i.e., reduced form of glutathione, uric acid) in the blood of the supplemented individuals are taken into account (Veskoukis et al., 2020; Margaritelis et al., 2018).

36.5.2 Sociomarkers and biomarkers: the nutritional approach

In the next three paragraphs, the sociological aspect of the complicated role of nutrition on human health when combined with xenobiotic administration will be analyzed and its significance will be advanced (Fig. 36.2). In fact, the evaluation of the effects of nutrition is carried out with the measurement of specific surrogate endpoints, which are biological markers or biomarkers (Veskoukis et al., 2019). When examining how nutrition affects redox homeostasis, redox biomarkers are adopted, a practice that has been defined as the *biomarker issue* (Veskoukis et al., 2019). It may look like redox biology and toxicology are going retro, but the approach of measuring redox biomarkers is utterly correlated to the sociological aspect of biological sciences, as it will be shown herein (Margaritelis et al., 2016; Ghiara and Russo, 2019). The definition of the term *redox biomarker* has been given recently (Veskoukis et al., 2019). The sociomarkers, on the other hand, have also been characterized as social measures that allow researchers to comprehend how social parameters (i.e., nutrition, poverty, financial condition) affect the biology of human organisms individually (Ghiara and Russo, 2019; Ghiara, 2020). If we try to parallelize biomarkers and sociomarkers, it could be concluded that biomarkers can be used in order to reveal the cause-effect relation of exposure to xenobiotics with disease onset on the biological level, whereas sociomarkers offer a sociological extension to this notion. It is worth mentioning that the

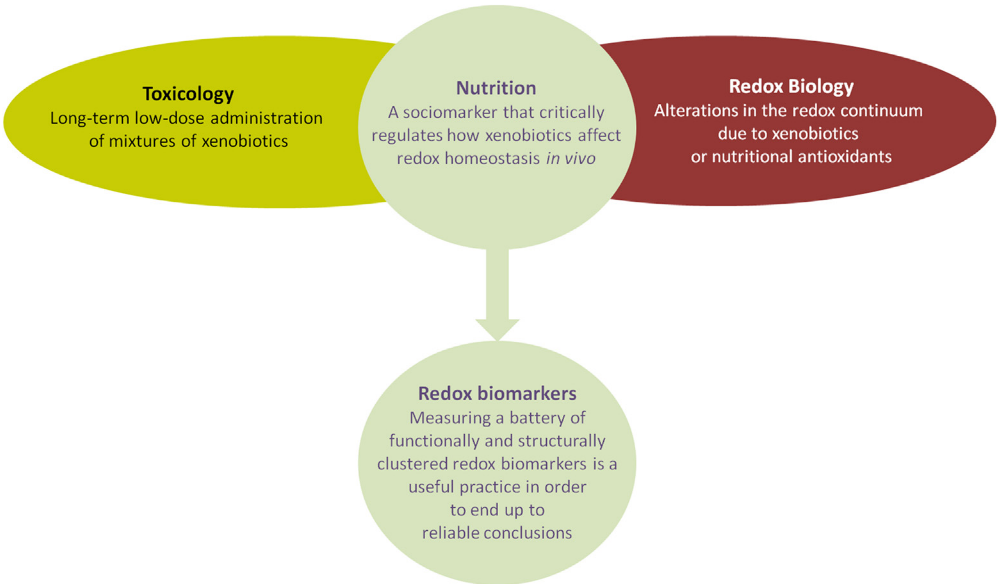

FIGURE 36.2 Nutrition in the middle of a continuum formulated by toxicology and redox biology. Nutrition is a sociomarker and a decisive factor for the evaluation of the effects of xenobiotic administration on redox homeostasis. Redox biomarkers, when sorted in functional and structural groups, exert translational potency.

idea of adopting sociomarkers tackles a common obstacle, which is the *measurement of the social* (Ghiara and Russo, 2019).

This interplay between socio- and biomarkers probably seems extraordinary in the eyes of a natural scientist. However, it is indisputable that social sciences can serve as a precious partner in order the researchers to evaluate pillars of nutrition (i.e., antioxidant supplementation, nutritional habits) that determine the final outcome of toxic agent administration on the redox continuum. Several studies have shown such an interplay. Particularly, the nutritional habits of individuals can be affected directly or indirectly by differential social factors, and are also probably characterized as both sociomarkers and social determinants (Braveman et al., 2011). To that end, the alterations of nutritional background due to sociomarkers can contribute to detrimental or beneficial changes of systemic and tissue redox status. This idea is in parallel with the *meet-in-the-middle* biomarker concept introduced by Vineis and Perera (2007). This is a concept referring to how specific (redox) biomarkers could acquire clinical relevance, which is a question without an answer so far (Veskoukis et al., 2020). In detail, biomarkers altered in retrospective studies (which move from back to forth examining effects of a treatment on specific biomarkers during a long or shorter period of time) could form a causal relation with certain diseases if these biomarkers are also related to these pathologies in prospective studies (which move from forth to back examining effects of a treatment on specific biomarkers in subjects that have been treated and others that constitute the control group) during a long or shorter period of time (Vineis and Perera, 2007). Thus the clinical significance is assessed in the middle of the route between a prospective and a retrospective experimental approach. Being on the same page, the altered redox biomarkers after xenobiotic administration (moving from back to forth) should be more correctly evaluated in terms of their clinical significance if the nutritional habits of the baseline values of systemic antioxidants of the subjects are taken into account (moving for forth to back). This *meet-in the-middle* notion that introduces the essential role of a sociomarker (i.e., nutrition) in the manifestation of the putative alterations of redox status after exposure to xenobiotics gives the opportunity to make one step forward toward answering the question whether specific redox biomarkers exert clinical significance (Vineis and Perera, 2007; Veskoukis et al., 2020). In this case, this concept is introduced by the author as the *pendulum-like methodological concept* for evaluating the putative clinical significance of redox biomarkers, on the basis of the biomarker-issue notion integrating the research areas of toxicology, redox biology, and nutrition. This concept is depicted in Fig. 36.3.

The sociological aspect of biology under the frame of the biological action of xenobiotics guided by nutrition is an interesting idea that will probably lead to the answer of crucial questions in the related fields. Insightful studies have correlated biomarkers, namely inflammatory indices that are conterminous to redox biomarkers with social factors indicating sociomarkers as basic pillars at the epistemological level of redox biology and toxicology (Castagné et al., 2016). The association of social aspects with disease etiology has also been proposed showing an inextricable link

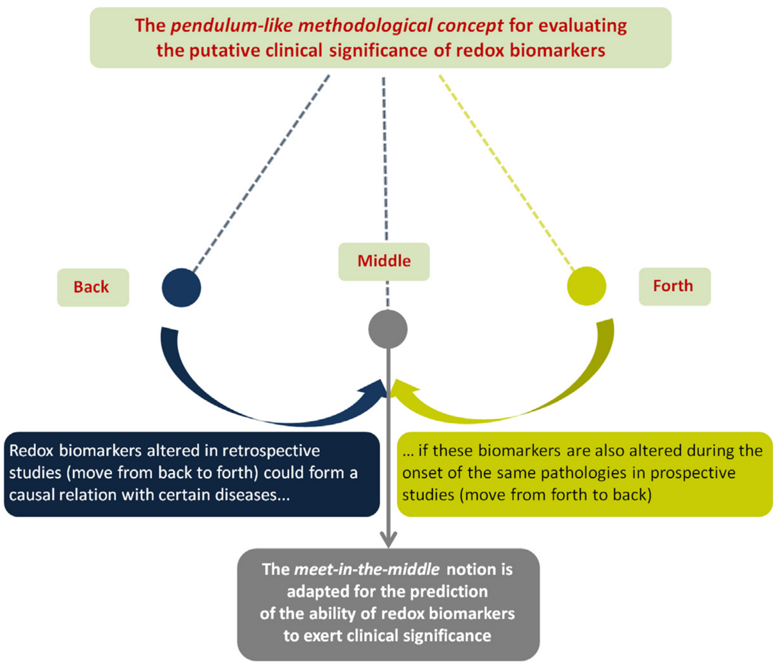

FIGURE 36.3 The pendulum-like methodological concept. A conceptual model that incorporates the *meet-in-the-middle* notion, as introduced by Vineis and Perera (2007), in order to offer a clue for the evaluation of the putative clinical significance of redox biomarkers.

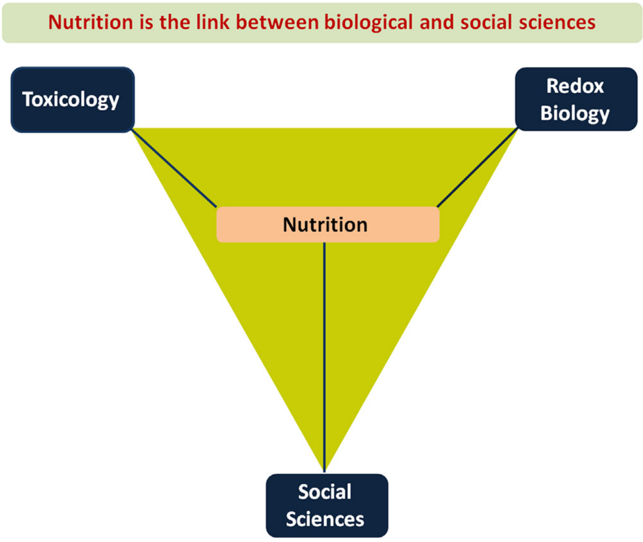

FIGURE 36.4 The link between biological and social sciences. Several queries of the biological sciences can be addressed under the frame of social sciences: Nutrition appears to be the link.

between sociomarkers and pathology, parallelized in our case with nutrition or diet and toxicity of xenobiotics examined in the frame of a redox-related outcome (Berkman et al., 2000; Vineis et al., 2017; Kelly and Russo, 2017; Ghiara and Russo, 2019). It is concluded that although the sociological approach of toxicology and redox biology, considering nutrition as the link between biological and social sciences, is at its nascent stages it is worth examining this aspect as it is anticipated to offer mechanistic answers (Fig. 36.4).

36.6 Concluding remarks

Toxicology, redox biology, and nutrition are interrelated research disciplines. A key effect of xenobiotic administration under the long-term, low-dose regimen as dictated by the perception shift in the ideas of modern toxicology (i.e., the *real-life risk simulation* or, alternatively, the *real-life exposure scenario* concept) is the alteration of redox equilibrium. Redox biomarkers are usually measured in order to evaluate this effect, taking into account nutrition, which is a decisive sociomarker for ending up at safe, clinically relevant conclusions. However, the clinical relevance of redox biomarkers has not yet been established, since it has been shown that several redox biomarkers are the outcome of several redox-related pathologies, although their cause-effect relation to clinical outcomes has not been proven. Therefore a new conceptual model, called the *pendulum-like methodological concept*, was introduced herein in order to offer a clue toward the evaluation of the putative clinical significance of redox biomarkers.

References

Berkman, L.F., Glass, T., Brissette, I., Seeman, T.E., 2000. From social integration to health: Durkheim in the new millennium. Soc. Sci. Med. 51 (6), 843−857.

Biomarkers Definitions Working Group, 2001. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin. Pharmacol. Ther. 69 (3), 89−95.

Braveman, P., Egerter, S., Williams, D.R., 2011. The social determinants of health: coming of age. Annu. Rev. Public. Health 32, 381−398.

Cairns, S.P., 2006. Lactic acid and exercise performance: culprit or friend? Sports Med. 36 (4), 279−291.

Campion, S., Aubrecht, J., Boekelheide, K., Brewster, D.W., Vaidya, V.S., Anderson, L., et al., 2013. The current status of biomarkers for predicting toxicity. Expert. Opin. Drug. Metab. Toxicol. 9 (11), 1391−1408.

Castagné, R., Delpierre, C., Kelly-Irving, M., Campanella, G., Guida, F., Krogh, V., et al., 2016. A life course approach to explore the biological embedding of socioeconomic position and social mobility through circulating inflammatory markers. Sci. Rep. 6, 25170.

Deavall, D.G., Martin, E.A., Horner, J.M., Roberts, R., 2012. Drug-induced oxidative stress and toxicity. J. Toxicol. 2012, 645460.

Docea, A.O., Calina, D., Goumenou, M., Neagu, M., Gofita, E., Tsatsakis, A., 2016. Study design for the determination of toxicity from long-term-low-dose exposure to complex mixtures of pesticides, food additives and lifestyle products. Toxicol. Lett. 258, S179-S.

Docea, A.O., Gofita, E., Goumenou, M., Calina, D., Rogoveanu, O., Varut, M., et al., 2018. Six months exposure to a real life mixture of 13 chemicals' below individual NOAELs induced non monotonic sex-dependent biochemical and redox status changes in rats. Food Chem. Toxicol. 115, 470−481.

Docea, A.O., Goumenou, M., Calina, D., Arsene, A.L., Dragoi, C.M., Gofita, E., et al., 2019. Adverse and hormetic effects in rats exposed for 12 months to low dose mixture of 13 chemicals: RLRS part III. Toxicol. Lett. 310, 70−91.

Draganidis, D., Karagounis, L.G., Athanailidis, I., Chatzinikolaou, A., Jamurtas, A.Z., Fatouros, I.G., 2016. Inflammaging and skeletal muscle: can protein intake make a difference? J. Nutr. 146 (10), 1940−1952.

ENTOX/TIWET (The Faculty of the Department of Environmental Toxicology and The Institute of Wildlife and Environmental Toxicology-Clemson University), 1996. Aquatic and terrestrial ecotoxicology. In: Klaassen, C.D. (Ed.), Casarett and Doull's Toxicology. The basic Science of Poisons, fiftieth ed. McGraw-Hill, United States, pp. 883−905.

Fountoucidou, P., Veskoukis, A.S., Kerasioti, E., Docea, A.O., Taitzoglou, I.A., Liesivuori, J., et al., 2019. A mixture of routinely encountered xenobiotics induces both redox adaptations and perturbations in blood and tissues of rats after a long-term low-dose exposure regimen: the time and dose issue. Toxicol. Lett. 317, 24−44.

Ghezzi, P., 2020. Environmental risk factors and their footprints in vivo—a proposal for the classification of oxidative stress biomarkers. Redox Biol. 34, 101442.

Ghezzi, P., Ghiara, V., Davies, K., 2020. Epistemological Challenges of the Oxidative Stress Theory of Disease and the Problem of Biomarkers. Oxidative Stress, Academic Press, London, pp. 13−27.

Ghiara, V., 2020. Disambiguating the role of paradigms in mixed methods research. J. Mix. Methods Res. 14 (1), 11−25.

Ghiara, V., Russo, F., 2019. Reconstructing the mixed mechanisms of health: the role of bio- and sociomarkers. Longitud. Life Course Stud. 10 (1), 7−25.

Giboney, P.T., 2005. Mildly elevated liver transaminase levels in the asymptomatic patient. Am. Fam. Physician 71 (6), 1105−1110.

Hathcock, J.N., 1990. Nutritional toxicology: basic principles and actual problems. Food Addit. Contam. 7 (Suppl. 1), S12−S18.

Jones, D.P., 2006. Redefining oxidative stress. Antioxid. Redox Signal. 8, 1865−1879.

Kelly, M.P., Russo, F., 2017. Causal narratives in public health: the difference between mechanisms of aetiology and mechanisms of prevention in noncommunicable diseases. Sociol. Health Illn. 40 (1), 82−99.

Kerasioti, E., Kiskini, A., Veskoukis, A., Jamurtas, A., Tsitsimpikou, C., Tsatsakis, A.M., et al., 2012. Effect of a special carbohydrate-protein cake on oxidative stress markers after exhaustive cycling in humans. Food Chem. Toxicol. 50 (8), 2805−2810.

Kerasioti, E., Veskoukis, A., Virgiliou, C., Theodoridis, G., Taitzoglou, I., Kouretas, D., 2019. The strong antioxidant sheep/goat whey protein protects against mTOR overactivation in rats: a mode of action mimicking fasting. Antioxidants (Basel) 8 (3), 71.

Kouka, P., Tekos, F., Papoutsaki, Z., Stathopoulos, P., Halabalaki, M., Tsantarliotou, M., et al., 2020. Olive oil with high polyphenolic content induces both beneficial and harmful alterations on rat redox status depending on the tissue. Toxicol. Rep. 7, 421−432.

Kourtzidis, I.A., Dolopikou, C.F., Tsiftsis, A.N., Margaritelis, N.V., Theodorou, A.A., Zervos, I.A., et al., 2018. Nicotinamide riboside supplementation dysregulates redox and energy metabolism in rats: Implications for exercise performance. Exp. Physiol. 103 (10), 1357−1366.

Le Gal, K., Ibrahim, M.X., Wiel, C., Sayin, V.I., Akula, M.K., Karlsson, C., et al., 2015. Antioxidants can increase melanoma metastasis in mice. Sci. Transl. Med. 7 (308), 308re8.

Margaritelis, N.V., Cobley, J.N., Paschalis, V., Veskoukis, A.S., Theodorou, A.A., Kyparos, S., et al., 2016. Going retro: oxidative stress biomarkers in modern redox biology. Free. Radic. Biol. Med. 98, 2−12.

Margaritelis, N.V., Paschalis, V., Theodorou, A.A., Kyparos, A., Nikolaidis, M.G., 2018. Antioxidants in personalized nutrition and exercise. Adv. Nutr. 9 (6), 813−823.

Nikolaidis, M.G., Margaritelis, N.V., 2018. Same redox evidence but different physiological "stories": the rashomon effect in biology. Bioessays 40 (9), e1800041.

Picó, C., Serra, F., Rodríguez, A.M., Keijer, J., Palou, A., 2019. Biomarkers of nutrition and health: new tools for new approaches. Nutrients 11 (5), 1092.

Silbergeld, E.K., Davis, D.L., 1994. Role of biomarkers in identifying and understanding environmentally induced disease. Clin. Chem. 40 (7), 1363−1367.

Spanidis, Y., Veskoukis, A.S., Papanikolaou, C., Stagos, D., Priftis, A., Deli, C.K., et al., 2018. Exercise-induced reductive stress is a protective mechanism against oxidative stress in peripheral blood mononuclear cells. Oxid. Med. Cell Longev. 2018, 3053704.

Sykiotis, G.P., Kalliolias, G.D., Papavassiliou, A.G., 2005. Pharmacogenetic principles in the Hippocratic writings. J. Clin. Pharmacol. 45 (11), 1218−1220.

Tsatsakis, A.M., Docea, A.O., Tsitsimpikou, C., 2016. New challenges in risk assessment of chemicals when simulating real exposure scenarios; simultaneous multi-chemicals' low dose exposure. Food Chem. Toxicol. 96, 174−176.

Tsatsakis, A.M., Kouretas, D., Tzatzarakis, M.N., Stivaktakis, P., Tsarouhas, K., Golokhvast, K.S., et al., 2017. Simulating real-life exposures to uncover possible risks to human health: a proposed consensus for a novel methodological approach. Hum. Exp. Toxicol. 36 (6), 554−564.

Tsatsakis, A.M., Vassilopoulou, L., Kovatsi, L., Tsitsimpikou, C., Karamanou, M., Leon, G., et al., 2018. The dose response principle from philosophy to modern toxicology: the impact of ancient philosophy and medicine in modern toxicology science. Toxicol. Rep. 5, 1107−1113.

Veskoukis, A.S., 2020. Redox signalling and antioxidant defence in pathogenic microorganisms: a link to disease and putative therapy. In: Preedy, V.R. (Ed.), Pathology: Oxidative Stress and Dietary Antioxidants. Academic Press, San Diego, CA, pp. 87−95.

Veskoukis, A.S., Nikolaidis, M.G., Kyparos, A., Kokkinos, D., Nepka, C., Barbanis, S., et al., 2008. Effects of xanthine oxidase inhibition on oxidative stress and swimming performance in rats. Appl. Physiol. Nutr. Metab. 33 (6), 1140−1154.

Veskoukis, A.S., Nikolaidis, M.G., Kyparos, A., Kouretas, D., 2009. Blood reflects tissue oxidative stress depending on biomarker and tissue studied. Free. Radic. Biol. Med. 47 (10), 1371−1374.

Veskoukis, A.S., Kyparos, A., Stagos, D., Kouretas, D., 2010. Differential effects of xanthine oxidase inhibition and exercise on albumin concentration in rat tissues. Appl. Physiol. Nutr. Metab. 35 (3), 244−250.

Veskoukis, A.S., Kyparos, A., Nikolaidis, M.G., Stagos, D., Aligiannis, N., Halabalaki, M., et al., 2012a. The antioxidant effects of a polyphenol-rich grape pomace extract in vitro do not correspond in vivo using exercise as an oxidant stimulus. Oxid. Med. Cell Longev. 2012, 185867.

Veskoukis, A.S., Tsatsakis, A., Kouretas, D., 2012b. Dietary oxidative stress and antioxidant defense with an emphasis on plant extract administration. Cell Stress. Chaperones 17 (1), 11−21.

Veskoukis, A.S., Kyparos, A., Paschalis, V., Nikolaidis, M.G., 2016a. Spectrophotometric assays for measuring redox biomarkers in blood. Biomarkers 21 (3), 208−217.

Veskoukis, A.S., Goutianos, G., Paschalis, V., Margaritelis, N.V., Tzioura, A., Dipla, K., et al., 2016b. The rat closely mimics oxidative stress and inflammation in humans after exercise but not after exercise combined with vitamin C administration. Eur. J. Appl. Physiol. 116 (4), 791−804.

Veskoukis, A.S., Margaritelis, N.V., Kyparos, A., Paschalis, V., Nikolaidis, M.G., 2018a. Spectrophotometric assays for measuring redox biomarkers in blood and tissues: the NADPH network. Redox Rep. 23 (1), 47−56.

Veskoukis, A.S., Paschalis, V., Kyparos, A., Nikolaidis, M.G., 2018b. Administration of exercise-conditioned plasma alters muscle catalase kinetics in rat: an argument for in vivo-like km instead of in vitro-like Vmax. Redox Biol. 15, 375−379.

Veskoukis, A., Kerasioti, E., Priftis, A., Kouka, P., Spanidis, Y., Makri, S., et al., 2019. A battery of translational biomarkers for the assessment of the in vitro and in vivo antioxidant action of plant polyphenolic compounds: the biomarker issue. Curr. Opin. Toxicol. 13, 99−109.

Veskoukis, A.S., Tsatsakis, A., Kouretas, D., 2020. Approaching reactive species in the frame of their clinical significance: a toxicological appraisal. Food Chem. Toxicol. 138, 111206.

Vineis, P., Perera, F., 2007. Molecular epidemiology and biomarkers in etiologic cancer research: the new in light of the old. Cancer Epidemiol. Biomark. Prev. 16, 1954−1965.

Vineis, P., Illari, P., Russo, F., 2017. Causality in cancer research: a journey through models in molecular epidemiology and their philosophical interpretation. Emerg. Themes Epidemiol. 14, 7.