Health Damage and Repair Mechanism Related to Formaldehyde Released from Wood-based Panels

Fan Gao,[a,#] Xiaohen Yue,[a,#] Hongqi Yang,[a,*] Yafeng Yang,[a,*] Su Shiung Lam,[b] Wanxi Peng,[a] and Xiangmeng Chen [a,*]

Wood-based panels, which contain wood raw materials along with urea-formaldehyde (UF) or phenol-formaldehyde (PF) resins, can increase the indoor air concentration of formaldehyde. Formaldehyde can stimulate the upper respiratory mucosa and cross-linking reaction with cell proteins and DNA, and this can result in degeneration and necrosis of respiratory cells and damaged cell proliferation. Formaldehyde can induce health hazards such as nasal cancer, leukemia, and destruction of the reproductive system. Acetaldehyde dehydrogenase 5 (ADH5) in the body cooperates with Fanconi anaemia complementation group D2 (FANCD2) to quickly metabolize formaldehyde into formate and maintain the balance of endogenous formaldehyde. However, when both ADH5 and FANCD2 proteins have defects or mutations, damaged DNA repair failure and cell proliferation induce a variety of health diseases. The damage has been found in the upper respiratory area, not on distal body tissues such as liver, kidney, and bone marrow. Meanwhile epidemiological survey has not shown a positive correlation between formaldehyde and health hazards. It is recommended that the use of wood formaldehyde-based products should be reduced, and pathogenesis genes and damage repair mechanism should be studied systematically and deeply to develop gene drugs to remove excess formaldehyde and activate the damage gene repair mechanism in the future.

DOI: 10.15376/biores.18.1.Gao

Keywords: Formaldehyde; Wood-based panel; Carcinogen; Health hazards; Leukemia; Gene therapeutic drugs

*Contact information: a: School of Forestry, Henan Agricultural University, Zhengzhou, 450002, China; b: Pyrolysis Technology Research Group, Institute of Tropical Aquaculture and Fisheries (AKUATROP), Universiti Malaysia Terengganu, 21030 Kuala Nerus, Terengganu, Malaysia; #These authors contributed equally to this work and act as co-first authors; *Corresponding authors: yhq0373342@henau.edu.cn (Hongqi Yang); yangyafengzz@163.com (Yafeng Yang); xmchen0610@163.com (Xiangmeng Chen)*

INTRODUCTION

Formaldehyde is contained in various wood bio-based products that are processed in the construction industry and light industry, such as wood raw materials/UF (urea-formaldehyde) or wood raw materials/PF (phenol-formaldehyde) (Dunky 1998; Kim *et al.* 2011). The annual output of woody formaldehyde bio-based products containing only formaldehyde is over 300 million m^3. In addition, low-concentration formaldehyde is used for disinfection of public places, as it reduces droplet-borne diseases such as influenza and Covid-19 due to absorption on surfaces facilitating long-term disinfection (Patterson *et al.* 2020). However, as a ubiquitous indoor air pollutant, formaldehyde is released from formaldehyde-based products such as woody products and electronics (Quievryn and Zhitkovich 2000; Lefebvre *et al.* 2012; Gudmundsson *et al.* 2019).

In recent years, the preparation method and performance of thermoplastic adhesive wood-based panels have been improved (Lu *et al.* 2017). The long-term problem of formaldehyde emission can be effectively improved through improving hot pressing technology, modification of adhesives, and developments in wood-based panel post-processing technology (Basta *et al.* 2006; Mo *et al.* 2022). The use of nanotechnology materials, reduction of formaldehyde-urea molar ratio, and usage of formaldehyde scavengers can reduce free formaldehyde emissions (Costa *et al.* 2013; Gangi *et al.* 2013; Moubarik *et al.* 2013; Pizzi *et al.* 2020; Antov *et al.* 2021a,b,c; Bekhta *et al.* 2021a,b; Selakjani *et al.* 2021; Dorieh *et al.* 2022a; Dorieh *et al.* 2022b; Kristak *et al.* 2022; Kristak *et al.* 2022). Post-treatment techniques such as veneer and edging can also effectively reduce the formaldehyde emissions rate (Roffael 2011; Costa *et al.* 2013; Bekhta *et al.* 2018). But most of the methods cannot be industrialized, and there is no way to completely solve the free formaldehyde (Antov *et al.* 2022; Kristak *et al.* 2022). Therefore, formaldehyde emission is still one of the main disadvantages and a major source of indoor air pollution (Dorieh *et al.* 2022a).

Inhaling airborne formaldehyde causes irritant responses in the upper respiratory tract, including nasal cavities and alveolar epithelia (Ezratty *et al.* 2007). Acetaldehyde dehydrogenase in the human body quickly metabolizes exogenous formaldehyde into formate and excretes it out of the body, maintaining the balance of endogenous formaldehyde to prevent genotoxic hazards. Long-term inhalation of high concentration formaldehyde increases the risk of protein cross-linking, including amino acid and ribonucleic acids, which has irreversible effects on immunity and genetics. Formaldehyde exposure could result in degeneration and necrosis of respiratory cells, damaged cell proliferation, and cancers (Taskinen *et al.* 1999; Qin *et al.* 2020). Triggered by the reclassification of formaldehyde as a carcinogenic substance (Mantanis *et al.* 2018), formaldehyde-based products have declined in popularity. Therefore, the correct understanding of the mechanism of formaldehyde inhalation and metabolism, gene damage and repair, and treatment and preventive measures are important in order to treat formaldehyde pollutants effectively (Ai *et al.* 2019).

Sources of Indoor Formaldehyde

Formaldehyde is a ubiquitous product in nature that can be produced by high-energy carbon dioxide and water under the photooxidation of sunlight, and it is a by-product of forest fires (Kim *et al.* 2011). Formaldehyde is released from plant stimulants, disinfectants, and nitrogen fertilizer used in agriculture (Salthammer and Gunschera 2021). In addition, formaldehyde results from fuel combustion, tobacco smoke, and the chemical industry (Gustafson *et al.* 2005). Formaldehyde-based fungicides and personal care products such as shampoo and cosmetics also release formaldehyde (Abe *et al.* 2020; Lopez-Sanchez *et al.* 2021). Formaldehyde is a natural compound in many plant-based foods (Blunden *et al.* 1998; Dhareshwar and Stella 2008; Jung *et al.* 2021; Silva *et al.* 2021).

The main sources of indoor formaldehyde are formaldehyde-based products (Table 1), which include wood-based panels, paints, furniture, carpeting, drapery fabric, building insulation materials, and electronic products. The release period of some products is more than 3 years. The highest formaldehyde emissions appear in summer and in airtight dry spaces (Kelly *et al.* 1999; Wiglusz *et al.* 2002; Kim and Kim 2005; Kim *et al.* 2011).

Table 1. Formaldehyde Emission Rate of Consumer Products

Products	Emission Rate ($\mu g/m^2 \cdot hr$)	References
Bare urea–formaldehyde wood products	9 - 1578	(Wiglusz *et al.* 2002)
Coated urea−formaldehyde wood products	1 - 461	(Wiglusz *et al.* 2002)
Permanent press fabrics	42 - 214	(Kim and Kim 2005)
Decorative laminates	4 - 50	(Kim and Kim 2005)
Fiber glass products	16 - 32	(Kim and Kim 2005)
Paper grocery bags and towels	0.5 - 0.6	(Kelly *et al.* 1999)

Hazards of Formaldehyde Exposure

Formaldehyde is a toxic one-carbon compound having high water solubility and high reactivity; its half-life in blood is 1 to 1.5 min. Epidemiological investigation and in-depth research of formaldehyde exposure show that formaldehyde results in many kinds of health hazards. The hazardous effects of inhalation different concentrations of formaldehyde on humans and several kinds of species are shown in Table 2 (Kane and Alarie 1977; Wartew 1983).

For most people, small amounts of formaldehyde gas do not irritate eyes and nasal cavity, while short-time exposure to formaldehyde affect respiratory mucosa membrane and damage the cornea, resulting in tears and vision loss (Aerts *et al.* 2020). Repeated formaldehyde exposure and contact with skin may lead to development of severe dermatitis, bronchitis, and asthma with significant clinical respiratory disease, including pronounced lachrymation, pulmonary oedema, and pneumonitis (Bryson *et al.* 1981; Wartew 1983). In some, tolerance develops. If a large amount of formaldehyde solution is ingested accidentally, formaldehyde is rapidly metabolized into formic acid, leading to serious acidosis, causing corrosion to the upper digestive tract and ultimately death. A study of leukaemia and nasopharyngeal carcinoma of more than 50,000 professional workers of formaldehyde exposure for up to 60 years clearly shows that occupational exposure to formaldehyde was not the inducement of leukemia and nasopharyngeal carcinoma, but the proportion of patients exposed to formaldehyde is high (Coggon *et al.* 2003; Kathleen 2003; Golden 2011).

Acetaldehyde dehydrogenase (ADH5) in the body metabolizes formaldehyde into formate, water, and carbon dioxide, which are excreted with urine (Heck *et al.* 1985; Monticello *et al.* 1996; Barber and Donohue 1998). Though inhalation of high formaldehyde concentrations may temporarily increase the endogenous formaldehyde level, a safe level could be maintained by the metabolic mechanism (Heck *et al.* 1990; Dhareshwar and Stella 2008; Agathokleous and Calabrese 2021). The irritation and damage of formaldehyde is concentrated in the respiratory and digestive tracts, but long-term indoor exposure increases the risk of insomnia, headaches, nasal cancer, and leukaemia (Møller 1980; Anonymous 1981; Bernardini *et al.* 1981; Tatsuo *et al.* 1999). Preventive measures, such as opening windows for ventilation, should be taken to avoid prolonged inhalation of formaldehyde.

Table 2. Effects of Formaldehyde Exposure by Inhalation and Acute Toxicity Dose

Species	HCHO Concentration (ppm)	Duration of Exposure	Effect	Acute Toxicity Dose (mg/kg)	Reference
Rat	3.8	90 days	1/15 died	36 (lowest lethal, Oral); 87 (death to 50%, intravenous)	(Kane and Alarie 1977; Wartew 1983)
	250	4 h	Fatal		(Kane and Alarie 1977; Wartew 1983)
	490-1388	0.5 h	Severe irritation of eye, nose and lung, listlessness		(Kane and Alarie 1977; Wartew 1983)
	815	0.5 h	Approximate death to 50% in three-week observation		(Kane and Alarie 1977; Wartew 1983)
Rabbit	3.8	90 days	Interstitial inflammation in lungs	270 (death to 50%, skin) 240 (lowest lethal, subcutaneous)	(Kane and Alarie 1977; Wartew 1983)
	15.5	Up to 10 h	3/5 died		(Kane and Alarie 1977; Wartew 1983)
Mouse	15.5	Up to 10 h	17/50 died	300 (death to 50%, subcutaneous); 16 (death to 50%, intraperitoneal)	(Kane and Alarie 1977; Wartew 1983)
	82	1 h/day, 3 days/week, up to 35 weeks	Normal weight gain		(Kane and Alarie 1977; Wartew 1983)
	163	1 h/day, 3 days/week, up to 35 weeks	Fatal, severe damage of trachea and major bronchi		(Kane and Alarie 1977; Wartew 1983)
	735	2 h	Fatal		(Kane and Alarie 1977; Wartew 1983)
Human	1	5 min	8% reported eye irritation	36 (lowest lethal, oral)	(Kane and Alarie 1977; Wartew 1983)
	2-4	5 min	33% reported eye irritation		(Kane and Alarie 1977; Wartew 1983)
	5	5 min	67% reported eye irritation		(Kane and Alarie 1977; Wartew 1983)
	4-5	10-30 min	Irritation and discomfort, tolerable or tolerance develops for some		(Kane and Alarie 1977; Wartew 1983)

Health Hazards Mechanisms of Formaldehyde Exposure

The hazards of formaldehyde mainly come from its effects on genetic material (Coggon *et al.* 2003). Formaldehyde has high reactivity, and any formaldehyde that is not metabolised can cause DNA-adducts (including DNA-protein and DNA interstrand crosslinks) (Tan *et al.* 2020). Formaldehyde reacts with common proteogenic amino acids and other nucleophilic amino acids at different rates through hydroxymethylation, cyclization, cross-linking or disproportionation, which have different stability and significant biochemical complexity. They play an important role in health, disease biology, and evolution (Kamps *et al.* 2019). The main formaldehyde cross-linking site is aminogroup ($-NH_2$) of histone lysine, and it only reacts with free amino groups at the denaturation sites (Van *et al.* 1975; Vaughn 1978). When excessive formaldehyde is not metabolized, formaldehyde is cross-linked preferentially at DNA denaturation sites and causes single-strand breaks in DNA and DNA-protein cross-linking, which leads to DNA damage, DNA repair inhibition, and chromosomal mutations. Formaldehyde is mutagenic and carcinogenic in *Drosophila* larvae, bacteria, fungi, and rodents, and it poses a potential carcinogenic risk to humans (Grafstrom *et al.* 1985; Solomon *et al.* 1988).

In experiments using [^{14}C]-labelled formaldehyde, 91% of the inhaled formaldehyde was metabolized in nasal mucosa, while 9% was covalently linked with DNA protein. After exposure to [^{14}C] formaldehyde by inhalation in rats, approximately 40% was respired as $^{14}CO_2$, 40% was cross-linked with macromolecules, and 20% was excreted as formate (Casanova 1989). Exogenous formaldehyde has little or no effect in distal organs such as spleen, kidney, liver, and bone marrow (Table 3) (Heck and Casanova 2004). It is a causative agent of carcinogenic genotoxicity in the nasal epithelium.

With the concentration increase of [^{13}C]-formaldehyde, the concentration of endogenous formaldehyde gradually stabilizes, but the total formaldehyde concentration in blood does not increase (Kleinnijenhuis *et al.* 2013; Swenberg *et al.* 2013). Endogenous formaldehyde is the main source of DNA deficiency and leukemia (Yu *et al.* 2015). Regardless of exposure time, endogenous DNA-protein cross-linking (DPCs) are found in all examined organs. In contrast, exogenous DPCs only are present in nasal tissues and not in the distal organs, suggesting that the distal organs are less damaged by exogenous formaldehyde (Thrasher and Kilburn 2001; Duong *et al.* 2011).

Alcohol dehydrogenase 5 (ADH5) is a formaldehyde-decomposing enzyme in the body. ADH5 metabolizes exogenous formaldehyde into formate, thus preventing DPCs. When the gene of ADH5 is defective or mutant, exogenous formaldehyde can lead to bone marrow failure (Tan *et al.* 2020). If this happens, Fanconi anemia complementation group D2 (FANCD2) protein repairs DNA lesions and prevents cell proliferation, thereby preventing leukaemia, liver dysfunction, and other diseases. Detoxification also produces benign 1 C units, which maintain basic metabolism (Lucas *et al.* 2015; Burgos-Barragan *et al.* 2017; Nadalutti *et al.* 2021). If ADH5 and FANCD2 proteins are defective or mutant at the same time, the repair of bone marrow will fail, and many diseases will be induced by exogenous formaldehyde (Fig. 1). Thus, exogenous formaldehyde has a long-term impact on humans with gene defects in ADH5 and FANCD2. As the nasal cavity is the first to be exposed to formaldehyde, the lesions of cell proliferation and dysplasia firstly occur in the nasal cavity and involved tumor development (Nishikawa *et al.* 2021). The incidence of nasal tumors is the highest.

Table 3. Formation of N^2-HOMe-dG Mono-Adducts and dG-Me-Cys in the Different Tissue of Rats

Tissues	N^2-HOMe-dG (adducts/10^7 dG)		dG-Me-Cys (crosslink/10^8 dG)		Reference
	Endogenous	Exogenous	Endogenous	Exogenous	
Nose	2.84±1.13[a]	2.84±1.13[a]	4.51±1.48[b]	2.46±0.44[b]	(Swenberg *et al.* 2013; Lai *et al.* 2016)
Nasal epithelium	2.82±0.76[b]	1.05±0.16[b]	6.5±0.30[c]	18.18±7.23[c]	(Lai *et al.* 2016)
Liver	1.80±0.02[b]	1.97±0.38[b]	11.80±2.21[d]	NF	(Thrasher and Kilburn 2001; Lu *et al.* 2010; Lai *et al.* 2016)
Bone marrow	3.43±2.20[b]	NF	1.64±0.49[c]	NF	(Thrasher and Kilburn 2001; Lai *et al.* 2016)
Blood	2.49±0.50[b]	NF	4.98±0.61[c]	NF	(Lai *et al.* 2016)
Lung	2.13±0.26[b]	NF	-	-	(Lu *et al.* 2010; Yu *et al.* 2015)
Kidney	1.99±0.09[b]	NF	-	-	(Lu *et al.* 2010; Yu *et al.* 2015)
Spleen	1.83±0.25[b]	NF	-	-	(Lu *et al.* 2010; Yu *et al.* 2015)

Note: [a] Exposure for 5 days (10 ppm); [b] Exposure for 28 days (2ppm); [c] Exposure for 4 day (15 ppm); [d] Exposure for 2 day (6 ppm)； NF, not found

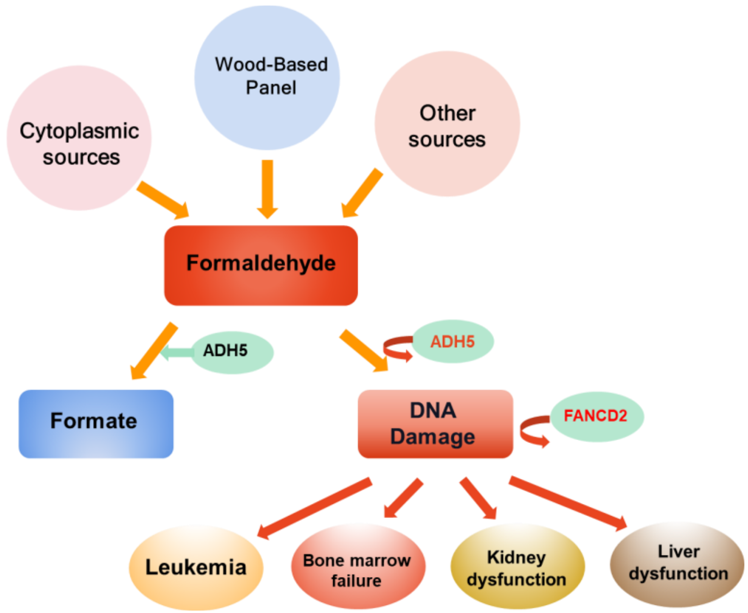

Fig. 1. Source of exogenous formaldehyde in body and deep hazards of lack of ADH5 and FANCD2 (Lucas *et al.* 2015, Creative Commons CC-BY)

Controversies of Formaldehyde Health Hazards

Formaldehyde exposure can induce obvious irritation, such as pronounced lachrymation, dizziness, loss of sense of smell, and pulmonary oedema. More importantly, it has strong and potential cytotoxicity and genetic toxicity and plays an important role in tissue carcinogenesis. Formaldehyde is a carcinogen and causative agent of human leukemia. Because formaldehyde is classified as a Group 1 carcinogen by the International Agency for Research on Cancer, there is popular worry about using woody formaldehyde bio-based products. Formaldehyde is listed as a major indoor pollutant by many countries (Chen *et al.* 2016). Many laws and regulations prohibit the addition of formaldehyde in food, cosmetics, and other products that are directly consumed and come into contact with the skin. Strict standards have been formulated for emissions from formaldehyde-based biopolymers in indoor and outdoor products. Excessive emission woody products are forbidden or reduced for use in indoor decoration, furniture, and other products. Although some studies have shown that the higher formaldehyde concentration in the environment and exposure time have an obvious relationship with the health effects of animals, the results and hypotheses cannot be fully applied to humans due to insufficient samples and the impossibility of effective human experiments. The positive correlation between exogenous formaldehyde and human health hazards cannot be concluded. Formaldehyde is not necessarily the basic reason of cause of nasopharyngeal carcinoma, leukemia, and reproductive defects (Marshall 1987; Vincent *et al.* 2004). Through the inhalation to labeling formaldehyde, the results show that formaldehyde has less or no effect on the distal body tissues such as bone marrow, liver, and kidney (Kang *et al.* 2021). When ADH5 and FANCD2 are deficient or defective, the formaldehyde hazards are increased, which indicates that gene defects may be the main pathogeny. Meanwhile, health hazards are closely related to other indoor air contaminants and lifestyle and health habits. The results of numerous studies on the health hazards of formaldehyde are basically based on the results of animal experiments and epidemiological research of human diseases, or some cases of mistaken ingestion of formaldehyde. Because of the great difference between humans and animals, and the inability of effective tests on human beings, it is impossible to study the hazards and mechanism of formaldehyde to human health. In addition, many studies have not fully demonstrated the health hazards of formaldehyde and there is a lack of effective research on the human body, which is also the focus of controversy, and have different opinions (Bryson *et al.* 2003; Nielsen *et al.* 2017). But there is a consensus on the potential hazards of high concentration and long-term exposure. Therefore, it is not necessary to panic too much about formaldehyde, and it is important to take correct preventive measures to reduce indoor formaldehyde concentration and exposure time.

Discussion and Conclusions

Numerous studies have shown that formaldehyde has potential genotoxicity. Excessive formaldehyde has adverse effects on genome stability and normal cell functions, such as causing the human body to be unable to metabolize normally, leading to DNA damage, repair inhibition, and chromosome mutation. Long-term exposure to high concentrations of formaldehyde will increase the risk of nasopharyngeal carcinoma, leukemia, and reproductive defects. In order to reduce the concentration of formaldehyde in indoor air, it is necessary to accelerate the research on wood products without and with low formaldehyde. By controlling the production and degradation process of formaldehyde, the metabolic stability of formaldehyde in the body can be maintained and formaldehyde imbalance can be prevented.

At present, the research on reducing or eliminating formaldehyde emissions from wood-based panels mainly focuses on reducing the molar ratio of formaldehyde to urea, improving the hot-pressing process, adding formaldehyde scavengers, post-processing technology, and using an alternative adhesive. However, formaldehyde emissions cannot be completely eliminated. Therefore, it is necessary to further strengthen the research on reducing the formaldehyde emissions of wood-based panels and indoor formaldehyde removal technology to reduce indoor formaldehyde concentration. Meanwhile, the epidemiology of formaldehyde hazards, formaldehyde pathogenesis genes and damage repair mechanism should be studied systematically, which can help to develop gene drugs to remove excess formaldehyde and activate the damage gene repair mechanism and void the harm of formaldehyde to health in the future.

Declaration of Competing Interest

All authors confirm that there is no conflict of interest for this research work and publication of this paper.

REFERENCES CITED

Abe, Y., Kobayashi, N., Yamaguchi, M., Mutsuga, M., Ozaki, A., Kishi, E., and Sato, K. (2020). “Determination of formaldehyde and acetaldehyde levels in poly (ethylene terephthalate) (PET) bottled mineral water using a simple and rapid analytical method,” *Food Chemistry* 344, article 128708. DOI: 10.1016/j.foodchem.2020.128708

Aerts, O., Dendooven, E., Foubert, K., Stappers, S., Ulicki, M., and Lambert, J. (2020). “Surgical mask dermatitis caused by formaldehyde (releasers) during the COVID pandemic,” *Contact Dermatitis* 83(2), 172-173. DOI: 10.1111/cod.13626

Agathokleous, E., and Calabrese, E. J. (2021). "Formaldehyde: Another hormesis-inducing chemical," *Environmental Research* 199, article 111395. DOI: 10.1016/j.envres.2021.111395

Ai, L., Tan, T., Tang, Y. H., Yang, J., Cui, D. H., Wang, R., Wang, A. B., Fei, X. C., Di, Y. L., Wang, X. M., *et al.* (2019). "Endogenous formaldehyde is a memory-related molecule in mice and humans," *Communications Biology* 2(1), 446. DOI: 10.1038/s42003-019-0694-x

Anonymous. (1981). "The health hazards of formaldehyde," *The Lancet* 317(8226), 926-927. DOI: 10.1016/S0140-6736(81)91623-8

Antov, P., Kristak, L., Reh, R., Savov, V., and Papadopoulos, A. N. (2021a), "Eco-friendly fiberboard panels from recycled fibers bonded with calcium lignosulfonate," *Polymers* 13(4), article 639. DOI: 10.3390/polym13040639

Antov, P., Savov, V., Kristak, L., Reh, R., and Mantanis, G. I. (2021b). "Eco-friendly, high-density fiberboards bonded with urea-formaldehyde and ammonium lignosulfonate," *Polymers* 13(2), article 220. DOI: 10.3390/polym13020220

Antov, P., Savov, V., Trichkov, N., Kristak, L., Reh, R., Papadopoulos, A. N., Taghiyari, H. R., Pizzi, A., Kunecova, D., and Pachikova, M. (2021c). "Properties of high-density fiberboard bonded with urea-formaldehyde resin and ammonium lignosulfonate as a bio-based additive," *Polymers* 13(16), article 2775. DOI: 10.3390/polym13162775

Antov, P., Seng H. L., Muhammad A. R. L., and Sumit, M. Y. (2022). "Potential of nanomaterials in bio-based wood adhesives: An overview," *Emerging Nanomaterials* 25-63. DOI: 10.1007/978-3-031-17378-3_2

Barber, R. D., and Donohue, T. J. (1998). "Pathways for transcriptional activation of a glutathione-dependent formaldehyde dehydrogenase gene," *Journal of Molecular Biology* 280(5), 775-784. DOI: 10.1006/jmbi.1998.1900

Basta, A. H., El-Saied, H., and Gobran, R. H. (2006). "Enhancing environmental performance of formaldehyde-based adhesives in lignocellulosic composites, Part III: Evaluation of some starch derivatives," *Designed Monomers and Polymers* 9(4), 325-347. DOI: 10.1163/156855506777952138

Bekhta, P., Sedliacik, J., and Jones, D. (2018). "Effect of short-term thermomechanical densification of wood veneers on the properties of birch plywood," *European Journal of Wood and Wood Products* 76(2), 549-562. DOI: 10.1007/s00107-017-1233-4

Bekhta, P., Noshchenko, G., Reh, R., Kristak, L., Sedliacik, J., Antov, P., Mirski, R., and Savov, V. (2021a). "Properties of eco-friendly particleboards bonded with lignosulfonate-urea-formaldehyde adhesives and pMDI as a crosslinker," *Materials* 14(17), article 4875. DOI: 10.3390/ma14174875

Bekhta, P., Sedliacik, J., Noshchenko, G., Kacik, F., and Bekhta, N. (2021b). "Characteristics of beech bark and its effect on properties of UF adhesive and on bonding strength and formaldehyde emission of plywood panels," *European Journal of Wood and Wood Products* 79(2), 423-433. DOI: 10.1007/s00107-020-01632-8

Bernardini, P., Carelli, G., and Valentino, R. (1981). "Formaldehyde in insulated housing," *The Lancet* 318(8242), 375-375. DOI: 10.1016/S0140-6736(81)90702-9

Blunden, G., Carpenter, B. G., Adrian-Romero, M., Yang, M. H., and Tyihak, E. (1998). "Formaldehyde in the plant kingdom," *Acta Biologica Hungarica* 49(2-4), 239-46.

Bryson, D. D., Berger J. M., and Lamm, S. H. (1981). "Health hazards of formaldehyde," *The Lancet* 317(8232), 1263-1264. DOI: 10.1016/S0140-6736(81)92432-6

Burgos-Barragan, G., Wit, N., Meiser, J., Dingler, F. A., Pietzke, M., Mulderrig, L., Pontel, L. B., Rosado, I. V., Brewer, T. F., Cordell, R. L., and *et al.* (2017). "Mammals divert endogenous genotoxic formaldehyde into one-carbon metabolism," *Nature* 548(7669), 549-554. DOI: 10.1038/nature23481

Casanova, M., Deyo, D. F., and Heck, H. D. (1989). "Covalent binding of inhaled formaldehyde to DNA in the nasal mucosa of Fischer 344 rats: Analysis of formaldehyde and DNA by high-performance liquid chromatography and provisional pharmacokinetic interpretation," *Fundam. Appl. Toxicol*. 12(3), 397-417. DOI: 10.1016/0272-0590(89)90015-8

Chen, M. J., Lin, C. H., Lai, C. H., Cheng, L. H., Yang, Y. H., Huang, L. J., Yeh, S. H., and Hsu, H. T. (2016). "Excess lifetime cancer risk assessment of volatile organic compounds emitted from a petrochemical industrial complex," *Aerosol and Air Quality Research* 16, 1954-1966. DOI: 10.4209/aaqr.2015.05.0372

Coggon, D., Harris, E. C., Poole, J., and Palmer, K. T. (2003). "Extended follow-up of a cohort of british chemical workers exposed to formaldehyde," *Journal of the National Cancer Institute* 95(21), 1608-1615. DOI: 10.1093/jnci/djg046

Costa, N. A., Pereira, J., Ferra, J., Cruz, P., Martins, J., Magalhaes, F. D., Mendes, A., and Carvalho, L. H. (2013). "Scavengers for achieving zero formaldehyde emission of wood-based panels," *Wood Science and Technology* 47, 1261-1272. DOI: 10.1007/s00226-013-0573-4

Dhareshwar, S. S., and Stella, V. J. (2008). "Your prodrug releases formaldehyde: Should you be concerned? No!," *Journal of Pharmaceutical Sciences* 97(10), 4184-4193.DOI: 10.1002/jps.21319

Dorieh, A., Selakjani, P. P., Shahavi, M. H., Pizzi, A., Movahed, S. G., Pour, M. F., and Aghaei, R. (2022a). "Recent developments in the performance of micro/ nanoparticle-modified urea-formaldehyde resins used as wood-based composite binders: A review," *International Journal of Adhesion and Adhesives* 114. DOI: 10.1016/j.ijadhadh.2022.103106

Dorieh, A., Pour, M. F., Movahed, S. G., Pizzi, A., Selakjani, P. P., Kiamahalleh, M. V ., Hatefnia, H., Shahavi, M. H., and Aghaei, R. (2022b). "A review of recent progress in melamine-formaldehyde resin based nanocomposites as coating materials," *Progress in Organic Coatings* 165. DOI: 10.1016/j.porgcoat.2022.106768

Dunky, M. (1998). "Urea–formaldehyde (UF) adhesive resins for wood," *International Journal of Adhesion & Adhesives* 18(2), 95-107. DOI: 10.1016/S0143-7496(97)00054-7

Duong, A., Steinmaus, C., Mchale, C. M., Vaughan, C. P., and Zhang, L. (2011). "Reproductive and developmental toxicity of formaldehyde: A systematic review," *Mutation Research Reviews in Mutation Research* 728(3), 118-138. DOI: 10.1016/j.mrrev.2011.07.003

Ezratty, V., Bonay, M., Neukirch, C., Orset-Guillossou, G., Dehoux, M., Koscienlny, S., Cabanes, P. A., Lambrozo, J., and Aubier, M. (2007). "Effect of formaldehyde on asthmatic response to inhaled allergen challenge," *Environmental Health Perspectives* 115(2), 210-214. DOI: 10.1289/ehp.9414

Gangi, M., Tabarsa, T., Sepahvand, S., and Asghari, J. (2013). "Reduction of formaldehyde emission from plywood," *Journal of Adhesion Science and Technology* 27(13), 1407-1417. DOI: 10.1080/01694243.2012.739016

Golden, R. (2011). "Identifying an indoor air exposure limit for formaldehyde considering both irritation and cancer hazards," *Critical Reviews in Toxicology* 41(8), 672-721. DOI: 10.3109/10408444.2011.573467

Grafstrom, R. C., Curren, R. D., Yang, L. L., and Harris, C. C. (1985). "Genotoxicity of formaldehyde in cultured human bronchial fibroblasts," *Science* 228(4695), 89-91. DOI: 10.1126/science.3975633

Gudmundsson, G., Finnbjornsdottir, R. G., Johannsson, T., and Rafnsson, V. (2019). "Air pollution in Iceland and the effects on human health. Review," *Laeknabladid* 105(10), 443-452. DOI: 10.17992/lbl.2019.10.252

Gustafson, P., Barregård, L., Lindahl, R., and Sallstein, G. (2005). "Formaldehyde levels in Sweden: Personal exposure, indoor, and outdoor concentrations," *J. Expo. Sci. Environ. Epidemiol*. 15(3), 252-260. DOI: 10.1038/sj.jea.7500399

Heck, H. D., Casanova-Schmitz, M., Dodd, P. B., Schachter, E. N., Witek, T. J., and Tosun, T. (1985). "Formaldehyde (CH_2O) concentration in the blood of humans and Fischer-344 rats exposed to CH_2O under controlled conditions," *American Industrial Hygiene Association Journal* 46(1), 1-3. DOI: 10.1080/15298668591394275

Heck, D. A., Casanova, M., and Starr, T. B. (1990). "Formaldehyde toxicity – New understanding," *Critical Reviews in Toxicology* 20(6), 397-426.

Heck, H. D., and Casanova, M. (2004). "The implausibility of leukemia induction by formaldehyde: A critical review of the biological evidence on distant-site toxicity," *Regulatory Toxicology and Pharmacology* 40(2), 92-106. DOI: 10.1016/j.yrtph.2004.05.001

Jackson, V. (1978). "Studies on histone organization in the nucleosome using formaldehyde as a reversible cross-linking agent," *Cell* 15(3), 945-954. DOI: 10.1016/0092-8674(78)90278-7

Jung, H., Kim, S., Yoo, K., and Lee, J. (2021). "Changes in acetaldehyde and formaldehyde contents in foods depending on the typical home cooking methods," *Journal of Hazardous Materials* 414, article 125475. DOI: 10.1016/j.jhazmat.2021.125475

Kamps, J. J. A. G., Hopkinson, R. J., Schofield, C. J., and Claridge, T. D. W. (2019). "How formaldehyde reacts with amino acids," *Communications Chemistry* 2(1), 357-367. DOI: 10.1038/s42004-019-0224-2

Kane, L. E., and Alarie, Y. (1977). "Sensory irritation to formaldehyde and acrolein during single and repeated exposures in mice," *Am. Ind. Hyg. Assoc. J*. 38(10), 509-522. DOI: 10.1080/0002889778507665

Kang, D. S., Kim, H. S., Jung, J. H., Lee, C. M., Ahn, Y. S., and Seo, Y. R. (2021). "Formaldehyde exposure and leukemia risk: a comprehensive review and network-based toxicogenomic approach," *Genes and Environment* 43(1), 13. DOI: 10.1186/s41021-021-00183-5

Kathleen, N. (2003). "Formaldehyde link to cancer," *The Lancet Oncology* 4(12), 714. DOI: 10.1016/S1470-2045(03)01294-4

Kelly, T. J., Smith, D. L., and Satola, J. (1999). "Emission rates of formaldehyde from materials and consumer products found in California homes," *Environ. Sci. Technol*. 33(1), 81-88. DOI: 10.1021/es980592+

Kim, K., H, Jahan. S. A., and Lee, J. T. (2011). "Exposure to formaldehyde and its potential human health hazards," *Journal of Environmental Science & Health Part C Environmental Carcinogenesis Reviews* 29(4), 277-299. DOI: 10.1080/10590501.2011.629972

Kim, S., and Kim, H. J. (2005). "Comparison of formaldehyde emission from building finishing materials at various temperatures in under heating system," *Indoor Air* 15(5), 317-325. DOI: 10.1111/j.1600-0668.2005.00368.x

Kleinnijenhuis, A. J., Staal, Y. C. M., Duistermaat, E., Engel, R., and Woutersen, R. A. (2013). "The determination of exogenous formaldehyde in blood of rats during and after inhalation exposure," *Food and Chemical Toxicology* 52, 105-112. DOI: 10.1016/j.fct.2012.11.008

Kristak, L., Antov, P., Bekhta, P., Lubis, M. A. R., Iswanto, A. H., Reh, R., Sedliacik, J., Savov, V., Taghiyari, H. R., and Papadopoulos, A. N. (2022). "Recent progress in ultra-low formaldehyde emitting adhesive systems and formaldehyde scavengers in wood-based panels: a review," *Wood Material Science and Engineering* DOI: 10.1080/17480272.2022.2056080

Lai, Y. Q., Yu, R., Hartwell, H. J., Moeller, B. C., Bodnar, W. M., and Swenberg, J. A. (2016). "Measurement of endogenous versus exogenous formaldehyde-induced DNA-protein crosslinks in animal tissues by stable isotope labeling and ultrasensitive mass spectrometry," *Cancer Research* 76, 2652-2661. DOI: 10.1158/0008-5472.CAN-15-2527

Lefebvre, M. A., Meuling, W. J. A., Engel, R., Coroama, M. C., Renner, G., Pape, W., and Nohynek, G. J. (2012). "Consumer inhalation exposure to formaldehyde from the use of personal care products/cosmetics," *Regulatory Toxicology and Pharmacology* 63(1), 171-176. DOI: 10.1016/j.yrtph.2012.02.011

Lopez-Sanchez, L., Miralles, P., Salvador, A., Merino-Sanjuan, M., and Merino, V. (2021). "In vitro skin penetration of bronidox, bronopol and formaldehyde from cosmetics," *Regulatory Toxicology and Pharmacology* 122, article 104888. DOI: 10.1016/j.yrtph.2021.104888

Lucas, B. P., Ivan, V. R., Guillermo, B., Juan, I. G., Rui, Y., Mark, J. A., Gayathri, C., Verena, B., Wei, W., Limin, L., and *et al.* (2015). "Endogenous formaldehyde is a hematopoietic stem cell genotoxin and metabolic carcinogen," *Molecular Cell* 60(1), 177-188. DOI: 10.1016/j.molcel.2015.08.020

Lu, F., Xian, Q. X., Xue, H. W., Hong, C., and Xian, F. M. (2017). "Effects of surface modification methods on mechanical and interfacial properties of high-density polyethylene-bonded wood veneer composites," *Journal of Wood Science* 63(1),65-73. DOI: 10.1007/s10086-016-1589-9

Lu, K., Collins, L. B., Ru, H. Y., Bermudez, E., and Swenberg, J. A. (2010). "Distribution of DNA adducts caused by inhaled formaldehyde is consistent with induction of nasal carcinoma but not leukemia," *Toxicological Sciences* 116(2), 441-451. DOI: 10.1093/toxsci/kfq061

Mantanis, G. I., Athanassiadou, E. T., Barbu, M. C., and Wijnendaele, K. (2018). "Adhesive systems used in the European particleboard, MDF and OSB industries," *Wood Material Science and Engineering*13(2), 104-116. DOI: 10.1080/17480272.2017.1396622

Marshall, E. (1987). "EPA indicts formaldehyde, 7 years later," *Science* 236(4800), 381. DOI: 10.2307/1698986

Moller, J. O. (1980). "Cancer risk from formaldehyde," *The Lancet* 2(8192), 480-481. DOI: 10.1016/S0140-6736(80)91917-0

Monticello, T. M., Swenberg, J. A., Gross, E. A., Leininger, J. R., Kimbell, J. S., Seilkop, S., Starr, T. B., Gibson, J. E., and Morgan, K. T. (1996). "Correlation of regional and

nonlinear formaldehyde-induced nasal cancer with proliferating populations of cells," *Cancer Res*. 56(5), 1012-1022.
Moubarik, A., Mansouri, H. R., Pizzi, A., Allal, A., Charrier, F., Badia, M. A., and Charrier, B. (2013), "Evaluation of mechanical and physical properties of industrial particleboard bonded with a corn flour–urea formaldehyde adhesive," *Composites Part B-Engineering* 44(1), 48-51. DOI: 10.1016/j.compositesb.2012.07.041
Mo, X. F., Zhang, X. H., Fang, L., and Zhang, Y. (2022). "Research progress of wood-based panels made of thermoplastics as wood adhesives," *Polymers* 14(1), DOI: 10.3390/polym14010098
Nadalutti, C. A., Prasad, R., and Wilson, S. H. (2021). "Perspectives on formaldehyde dysregulation: Mitochondrial dna damage and repair in mammalian cells," *DNA Repair* 105, article 103134. DOI: 10.1016/j.dnarep.2021.103134
Nielsen, G. D., Larsen, S. T., and Wolkoff, P. (2017). "Re-evaluation of the WHO (2010) formaldehyde indoor air quality guideline for cancer risk assessment," *Archives of Toxicology* 91(1), 35-61. DOI: 10.1007/s00204-016-1733-8
Nishikawa, A., Nagano, K., Kojima, H., and Ogawa, K. (2021). "A comprehensive review of mechanistic insights into formaldehyde-induced nasal cavity carcinogenicity," *Regulatory Toxicology and Pharmacology* 123, article 104937. DOI: 10.1016/J.YRTPH.2021.104937
Patterson, E. I., Prince, T., Anderson, E. R., Casas-Sanchez, A., Smith, S. L., Cansado-Utrilla, C., Turtle, L., and Hughes, G. L. (2020). "Methods of inactivation of SARS-CoV-2 for downstream biological assays," *The Journal of Infectious Diseases* 222, 1462-1467. DOI: 10.1093/infdis/jiaa507
Petinarakism, J. H., and Kavvouras, P. K. (2006). "Technological factors affecting the emission of formaldehyde from particleboard," *Wood Research* 51(1), 31-40.
Pizzi, A., Papadopoulos, A., and Policardi, F. (2020). "Wood composites and their polymer binders," *Polymers* 12, article 1115. DOI: 10.3390/polym12051115
Qin, D. C., Guo, B., Zhou, J., Cheng, H. M., and Chen, X. K. (2020). "Indoor air formaldehyde (HCHO) pollution of urban coach cabins," *Scientific Reports* 10(1), 332. DOI: 10.1038/s41598-019-57263-4
Quievryn, G., and Zhitkovich, A. (2000). "Loss of DNA-protein crosslinks from formaldehyde-exposed cells occurs through spontaneous hydrolysis and an active repair process linked to proteosome function," *Carcinogenesis* 21(8), 1573-1580. DOI: 10.1093/carcin/21.8.1573
Roffael, E. (2011). "On the responsiveness of hardened UF-resins of different molar ratio towards ammonia fumigation," *European Journal of Wood and Wood Products* 69(4), 675-676. DOI: 10.1007/s00107-011-0564-9
Salthammer, T., and Gunschera, J. (2021). "Release of formaldehyde and other organic compounds from nitrogen fertilizers," *Chemosphere* 263, article 127913. DOI: 10.1016/j.chemosphere.2020.127913
Selakjani, P. P., Dorieh, A., Pizzi, A., Shahavi, M. H., Hasnkhah, A., Shekarsaraee, S., Ashouri, M., Movahed, S. G., and Abatari, M. N. (2021). "Reducing free formaldehyde emission, improvement of thickness swelling and increasing storage stability of novel medium density fiberboard by urea-formaldehyde adhesive modified by phenol derivatives," *International Journal of Adhesion and Adhesives* 111, article 102962. DOI: 10.1016/j.ijadhadh.2021.102962

Silva, A. F. S., Gonçalves, I. C., and Rocha, F.R. (2021). "Smartphone-based digital images as a novel approach to determine formaldehyde as a milk adulterant," *Food Control* 125, article 107956. DOI: 10.1016/j.foodcont.2021.107956

Solomon, M. J., Larsen, P. L., and Varshavsky, A. (1988). "Mapping protein-DNA interactions in vivo with formaldehyde: Evidence that histone H4 is retained on a highly transcribed gene," *Cell* 53(6), 937-947. DOI: 10.1016/S0092-8674(88)90469-2

Swenberg, J. A., Moeller, B. C., Lu, K., Rager, J. E., Fry, R. C., and Starr, T. B. (2013). "Formaldehyde carcinogenicity research: 30 years and counting for mode of action, epidemiology, and cancer risk assessment," *Toxicologic Pathology* 41(2), 181-189. DOI: 10.1177/0192623312466459

Tatsuo, S., Satoru, D., and Shinpei, T. (1999). "Effects of formaldehyde, as an indoor air pollutant, on the airway," *Allergology International* 48(3), 151-160. DOI: 10.1046/j.1440-1592.1999.00131.x

Tan, W., and Deans, A. J. (2020). "Formaldehyde causes bone marrow failure linked to transcriptional reprogramming or metabolic deficiency," *Molecular Cell* 80(6), 935-937. DOI: 10.1016/j.molcel.2020.11.042

Taskinen, H. K., Kyyronen, P., Sallmen, M., Virtanen, S. V., Liukkonen, T. A., Huida, O., Lindbohm, M. L., and Anttila, A. (1999). "Reduced fertility among female wood workers exposed to formaldehyde," *American Journal of Industrial Medicine* 36(1), 206-212.

Thrasher, J. D., and Kilburn, K. H. (2001). "Embryo toxicity and teratogenicity of formaldehyde," *Archives of Environmental Health: An International Journal* 56(4), 300-311. DOI: 10.1080/00039890109604460

Van, L. F., Jackson, J. F., and Weintraub, H. (1975). "Identification of specific crosslinked histones after treatment of chromatin with formaldehyde," *Cell* 5(1), 45-50. DOI: 10.1016/0092-8674(75)90090-2

Vincent, C., Yann, G., Robert, B., Kurt, S., Béatrice, S., and Fatiha, E. G., (2004). "Advice on formaldehyde and glycol ethers," *Lancet Oncology* 5(9), 528. DOI: 10.1016/S1470-2045(04)01562-1

Wartew, G. A. (1983). "The health hazards of formaldehyde," *Journal of Applied Toxicology* 3(3), 121-126. DOI: 10.1002/jat.2550030303

Wiglusz, R., Nikel, G., Igielska, B., and Sitko, E. (2002). "Volatile organic compound emissions from particleboard veneered with decorative paper foil," *Holzforschung* 56(1), 108–110. DOI: 10.1515/HF.2002.018

Yu, R., Lai, Y. Q., Hartwell, H. J., Moeller, B. C., Doyle-Eisele, M., Kracko, D., Bodnar, W. M., Starr, T. B., and Swenberg, J. A. (2015). "Formation, accumulation, and hydrolysis of endogenous and exogenous formaldehyde-induced DNA damage," *Toxicological Sciences* 146(1), 170-182. DOI: 10.1093/toxsci/kfv079

Article submitted: November 15, 2022; Peer review completed: December 31, 2022; Revised version received and accepted: January 5, 2023; Published: January 13, 2023.
DOI: 10.15376/biores.18.1.Gao