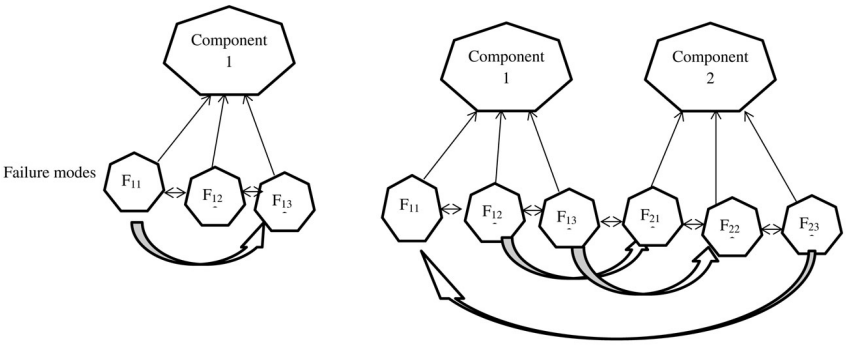

Figure 1. Internal failure causality relationships and external failure causality relationships (interaction between the failure modes).

technique for identifying, ranking and evaluating potential failures in new and existing products as well as in the improvement of product quality.

However, the FMEA method is limited when it comes to quantifying the failure causality relationships (FCRs) of the product components. Hence, applying the FMEA method in failure identification will produce incomplete analysis result of design risk for making a design decision, since one failure mode may exacerbate or result in another failure mode. Extensive literature of the failure analysis of parent product during redesigning of new product[4,5], shows that although the design risk of each failure mode of the product has been studied, no work has considered quantifying the FCRs of the product. Also, although some authors[6,7] have developed failure causality tools for machine maintenance, these tools were merely used for quantifying the internal failure causality relationships (IFCRs) within the components, without considering the external failure causality relationships (EFCRs) between components. Figure 1 shows the causality relationship (interaction of failure modes) of product components.

Thus, to build adequate design knowledge for the to-be-improved or redesigned product, the historical failure information of the parent or similar product should properly be analysed and the result converted into appropriate design knowledge. This can be achieved by simultaneous consideration of the root cause of failure, IFCR and EFCR between product components.

1. Kwapień, J. and Drożdż, S., *Phys. Rep*., 2012, **515**(3–4), 115–226; doi:10.1016/j.physrep.2012.01.007.
2. He, Y.-H., Wang, L.-B., He, Z.-Z. and Xie, M., *Eng. Appl. Artif. Intell*., 2015, **47**, 1–13; doi:10.1016/j.engappai.2015.06.002.
3. Bowles, J. B. and Pelaez, C. E., *Reliab. Eng. Syst. Saf*., 1995, **50**(2), 203–213; doi:10.1016/0951-8320(95)00068-D.
4. Zhao, H., You, J.-X. and Liu, H.-C., *Soft Comput*., 2016; doi:10.1007/s00500-016-2118-x.
5. Vahdani, B., Salimi, M. and Charkhchian, M., *Int. J. Adv. Manuf. Technol*., 2015, **77**(1–4), 357–368; doi:10.1007/s00170-014-6466-3.
6. Venkata Rao, R. and Gandhi, O. P., *Int. J. Mach. Tools Manuf*., 2002, **42**(4), 521–528; doi:10.1016/S0890-6955(01)00135-3.
7. Jangra, K., Grover, S., Chan, F. T. S. and Aggarwal, A., *Int. J. Adv. Manuf. Technol*., 2011, **56**(9–12), 959–974; doi:10.1007/s00170-011-3234-5.

DANIEL O. AIKHUELE*
FAIZ M. TURAN

Faculty of Manufacturing Engineering,
Universiti Malaysia Pahang,
Malaysia
**e-mail: danbishop_22@yahoo.co.uk*

Is the herbicide glyphosate really safe?

Glyphosate [*N*-(phosphonomethyl) glycine] is one of the most commonly used and largest selling herbicide worldwide. It is a non-selective (broad-spectrum), systemic and effective herbicide. Glyphosate was first registered by an US-based corporation in 1974. Since its introduction, the use of glyphosate has increased rapidly. Sharp rise in its use was also noticed with the introduction of genetically modified (GM) glyphosate-tolerant crops. It is registered for use in more than 130 countries. It controls annual and perennial weeds in various crops, orchards, plantations, pastures, lawns, gardens, forestry, roadsides and aquatic weeds. Glyphosate is rapidly translocated throughout the plant. The movement is mainly basipetal. It shows mobility through phloem, although mobility in xylem has also been reported. It tends to accumulate in plant regions with actively dividing cells. Glyphosate is soluble in water (12.0 g/litre). It inhibits the biosynthesis of aromatic amino acids, i.e. L-phenylalanine, L-tryptophan and L-tyrosine by inhibiting the shikimic acid pathway. This is done by competitively blocking the enzyme 5-enolpyruvylshikimate 3-phosphate synthase (EPSPS, E.C. 2.5.1.19), a key enzyme of the shikimic acid pathway. EPSPS is required in plants for synthesis of aromatic amino acids (L-tryptophan, L-phenylalanine and L-tyrosine) and other compounds, including vitamins, plant growth substance and lignin. These aromatic amino acids, besides being used for the synthesis of proteins, are also utilized as precursors of numerous natural products, such as pigments, alkaloids, hormones and cell-wall components in plants. Therefore inhibition of EPSPS (by glyphosate) can affect a number of physiological processes. Aspects like disease susceptibility and sprout suppression are also influenced by glyphosate treatment to the crop, depending on concentration and stage of growth[1]. Non-selective and systemic nature of this herbicide results in its residue in food and feed. Presently, maximum residue limit (MRL) for glyphosate ranges from 0.1 to 20 mg kg^{-1} (= 0.1 to 20 ppm) in different pulses, oil

and cereal crops[2]. MRL of 0.5 ppm has been reported for potato tubers by the European Union[3]. According to EXTOXNET[4], acceptable daily intake limit (ADIL) for glyphosate is 0.3 mg kg^{-1} of body wt day^{-1}. Since the target enzyme of glyphosate, i.e. EPSPS, is present only in plants and microorganisms, glyphosate-mediated inhibition of shikimic acid pathway occurs only in plants and microorganisms. In animals and humans, glyphosate is rapidly excreted unchanged. These reasons have been put forward in favour of glyphosate to elucidate its safer toxicological profile. Therefore, many impressive taglines have been used for glyphosate, such as 'global herbicide', 'once in-a-century herbicide' and 'less toxic than table salt'. However, Samsel and Seneff[5] provided evidence that glyphosate can mediate inhibition of cytochrome P450 enzyme in humans along with negative effect on the amino acid biosynthesis by the gut microbiome (mediated by the target enzyme of glyphosate). They are of the view that continuous and long-term exposure to glyphosate is responsible for some of the modern human diseases, including gastrointestinal disorders, obesity, diabetes, heart disease, depression, autism, infertility, cancer and Alzheimer's disease[5]. Further knowledge with respect to glyphosate in terms of its strong ability to chelate with iron, cobalt, molybdenum, copper and other rare metals and impairment of many cytochrome P450 enzymes (involved in detoxification of environmental toxins, activating vitamin D3, catabolizing vitamin A and maintaining bile acid production and sulphate supplies to the gut) showed its involvement in celiac disease and gluten intolerance[6]. Additionally, glyphosate contamination has contributed towards the increase in chronic and acute kidney failure, pancreatitis, different types of cancers, various disorders, especially to newborns, not only in humans, but in animals as well[7,8]. Another recently reported adverse impact of glyphosate is severe depletion of serum Mn and disruption of bile acid homeostasis and in this way glyphosate can promote autism, Alzheimer's disease, Parkinson's disease, anxiety disorder, osteoporosis, inflammatory bowel disease, renal lithiasis, osteomalacia, cholestasis, thyroid dysfunction and infertility[9]. All the above conditions can be substantially explained on the basis of defective regulation of Mn utilization in the body due to glyphosate[9]. Yet another recent report states that glyphosate causes large number of tumorigenic effects on biological systems, including direct damage to DNA in sensitive cells, disruption of glycine homeostasis, succinate dehydrogenase inhibition, chelation of manganese, modification to more carcinogenic molecules such as *N*-nitrosoglyphosate and glyoxylate, and disruption of fructose metabolism[10]. In view of all such reports, the World Health Organization has revised the assessment of carcinogenic potential of glyphosate in March 2015 and relabelled it as a 'probable carcinogen'[11,12]. It is also important to note that during the last few years some restrictions and bans have also came into force or are under consideration[13]. These include: (1) In June 2008, the government of the Canadian state Ontario passed an Act that among others prohibit's the use of glyphosate on lawns and gardens (www.beyondpesticides.org/dailynewsblog/?p=1351). (2) Denmark restricted glyphosate in September 2003 on the ground that it contaminates the drinking water resources[14]. (3) In April 2009, the Environmental Lawyers Association of Argentina filed a law suit seeking a ban on glyphosate, as a study by scientists showed malformations in amphibian embryos and hormone disrupting effects due to glyphosate[15,16]. In addition to this, other health problems were noticed in people living near the fields of glyphosate-resistant GM soybean[17]. (4) In a recent publication, Samsel and Seneff[18] have shown that glyphosate (a synthetic amino acid) acts as an amino acid analogue of glycine and thereby erroneously it can get misincorporated into polypeptide chains during protein synthesis. As a consequence of this, glyphosate accounts for multitude of diseases and conditions including diabetes, obesity, asthma, chronic obstructive pulmonary disease (COPD), pulmonary edema, adrenal insufficiency, hypothyroidism, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), Parkinson's disease, prion diseases, lupus, mitochondrial disease, non-Hodgkin's lymphoma, neural tube defects, infertility, hypertension, glaucoma, osteoporosis, fatty liver disease and kidney failure. The incidences of above diseases/conditions are also rising in many countries with the rise in the use of glyphosate on core/edible crops. (5) In a yet another recent development during 2016, European Union (EU) has decided that the European Chemicals Agency (ECHA) will conduct scientific investigations on glyphosate and till then the EU has refused to grant a new license to this product[19,20].

The above findings clearly show that all the known and probable concerns with respect to glyphosate and its use need greater attention. It has also become important that different regulatory and registration agencies should take the initiative and relook into the criteria on which parameters like MRL and ADIL are fixed, advocated and recommended. This needs to be done with a broader mindset and with more environment and eco-friendly attitude. Moreover, with advancements in knowledge and availability of clinical trials, the lucrative taglines may be shattered.

1. Paul, V., Ezekiel, R., Pandey, R. and Kumar, D., *Indian J. Plant Physiol.*, 2014, **19**, 293–305.
2. Pulse Canada, Glyphosate maximum residue limits (MRLs) fact sheet, Winnpeg, Manitoba, Canada, 2011; http://www.saskpulse.com/media/pdfs/110430FactSheetFinal.pdf.
3. MRL Status Report, Potatoes, European Union, 2007; http://www.nda.agric.za/docs/plantquality/Info%20HUB/Potatoes-%20files/Potatoes%20MRL%20Data-sheet.pdf
4. EXTOXNET, Pesticide information profile – glyphosate. Oregon State University, USA, 1996; http://extoxnet.orst.edu/pips/glyphosa.htm
5. Samsel, A. and Seneff, S., *Entropy*, 2013, **15**, 1416–1463.
6. Samsel, A. and Seneff, S., *Interdiscip. Toxicol.*, 2013, **6**, 159–184.
7. Hoy, J., Swanson, N. and Seneff, S., *Poult. Fish. Wildl. Sci.*, 2015, **3**, 1000132.
8. Seneff, S., Swanson, N., Li, C. and Koenig, G., *Agric. Sci.*, 2015, **6**, 1472–1501.
9. Samsel, A. and Seneff, S., *Surg. Neurol. Int.*, 2015, **6**, 45.
10. Samsel, A. and Seneff, S., *J. Biol. Phys. Chem.*, 2015, **15**, 121–159.
11. WHO, IARC Monographs Volume 112: Evaluation of Five Organophosphate Insecticides and Herbicides, World Health Organization, Geneva, 2015; http://www.iarc.fr/en/media-centre/iarcnews/pdf/MonographVolume112.pdf
12. Guyton, K. Z. *et al.*, *Lancet Oncology*, 2015, **16**, 490–491.
13. Thanal, Pesticide briefing – glyphosate and roundup, 2009; http://thanal.co.in/

uploads/resource/document/Pesticide-briefing--Glyphosate-14236639.pdf
14. GMWATCH, Danish water contaminated by roundup, ban imposed. Third World Network Biosafety Information Service, 2003; http://gmwatch.org/news/archive/2003/5029-glyphosate-ban-as-water-contaminated.
15. Ho, M. W., Glyphosate herbicide could cause birth defects – Argentina considers ban. Institute of Science in Society, London, 2009; http://www.i-sis.org.uk/GHCCBD.php
16. Ho, M. W., Ban glyphosate herbicides now – scientists confirm potent hormone disrupting effects, Institute of Science in Society, London, 2009; http://www.i-sis.org.uk/Ban_Glyphosate_Herbicides_Now.php
17. Misculin, N., Argentine herbicide lawsuit alarms soy farmers, 2009; http://www.reuters.com/article/us-argentina-herbicide-idUSTRE5464Q820090507
18. Samsel, A. and Seneff, S., *J. Biol. Phys. Chem.*, 2016, **16**, 9–46.
19. Alissa de Carbonnel, *Health News*, 6 June 2016; http://www.reuters.com/article/us-health-eu-glyphosate-idUSKCN0YS0Y0
20. Michalopoulos, S., *Agriculture and Food, News*, 12 July 2016; https://www.euractiv.com/section/agriculture-food/news/eu-agrees-ban-on-glyphosate-co-formulant/

VIJAY PAUL*
RAKESH PANDEY

Crop and Postharvest Physiology Lab,
Division of Plant Physiology,
ICAR-Indian Agricultural Research Institute,
New Delhi 110 012, India
**e-mail: vijay_paul_iari@yahoo.com*