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Structure–Toxicity Relationships of Acrylic Monomers

by John Autian*

Esters of acrylic acid, in particular methyl methacrylate, have wide applications in a number of industrial and consumer products, forming very desirable nonbreakable glass-like materials. In dentistry, the monomers are used to prepare dentures and a variety of filling and coating materials for the teeth. Surgeons utilize the monomers to prepare a cement which helps anchor prosthetic devices to bone. Special types of acrylic monomers such as the cyano derivatives have found a useful application as adhesive materials.

Most of the acrylic acid esters are volatile substances and can produce various levels of toxicity if inhaled. A large number of workers thus exposed to the vapors of these esters can develop clinical symptoms and signs of toxicity. This paper will discuss the toxicity of a large number of acrylic esters, and will attempt to show structure–activity relationships where such data are available. General comments will also be made as to the potential health hazards this variety of esters may present to selected segments of the population.

Introduction

Hundreds of millions of pounds of man-made polymeric materials belonging to the acrylic family are produced each year in this country for a host of industrial and consumer products. The glasslike appearance and nonbreakable property have made these plastics popular for the building, automotive, aerospace, and furniture industries. The dental and medical professions also use these materials for such items as denture plates, artificial teeth, and orthopedic cement. In fact, it perhaps can be said that no civilized man in his daily life is completely free from items prepared from an acrylic resin.

The main ingredient in the formation of an acrylic plastic is one of a number of acrylic acid esters, the primary ones being methyl methacrylate and methyl acrylate. Other analogs and homologs of the basic acrylic acid esters are also employed for specialized uses. These esters are the monomers which, when reacted with each other, produce the polymers known as the acrylic resins. For convenience, these polymers are prepared as powders or pellets which, in turn, are shipped to plastic companies for manufacture into the variety of commercial products alluded to earlier.

A very large number of workers in the plastic industry are exposed to acrylic monomers. At risk are also laboratory workers and health professions personnel in dental and surgical laboratories who use the acrylic monomers in preparation of medical and dental items. The widespread use of these monomers in industry and in certain laboratories raises questions pertinent to their toxicological properties and their short- and long-term health effects on persons exposed to them. Fortunately, because of adequate protection for industrial workers, few serious health problems have surfaced, but this may not necessarily mean that potential health problems do not exist, particularly with respect to long-term effects. Since most of the published toxicological data deal with the methyl acrylate and methyl

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methacrylate monomers, one should keep in mind that the other acrylic monomers may exhibit toxic properties not seen in the methyl esters. Relatively little toxicological information is available on these other monomers.

The major purpose of this paper is to review the toxicological aspects of acrylic monomers (excluding cyanoacrylates) and, where possible, to relate their activity to chemical structure or the physicochemical properties of the molecule. As will be seen, one section of this paper will deal with the use of mathematical models to help predict the toxic activity of a new or untested acrylic monomer and, further, to use this approach for speculation on the behavior of the compound in animals and humans. Finally, an assessment will be made of the real health threats presently existing for those people who have daily contact with these monomers.

Chemistry and Properties of Acrylic Monomers

The basic structure of acrylic monomers is the ester of acrylic acid:

$$CH=\underset{\displaystyle H}{\overset{\displaystyle |}{C}}-COOR$$

If R is a methyl group, the monomer, methyl acrylate, is produced. Replacement of the hydrogen with a methyl group forms the ester of methacrylic acid, and if R is again a methyl group, the most-used monomer in the acrylic series results, namely, methyl methacrylate. Various other types of monomers are possible by substitution of the R group with other functional groups. Even though methyl esters are used the most for production of acrylic resins, the ethyl, butyl, and several of the higher homologs in the series have special applications for polymers requiring certain unique properties.

The lower molecular weight acrylic monomers are liquids and have relatively lower boiling points and high vapor pressure. They have a characteristic odor, often extremely unpleasant. Commercial samples of the monomers generally require the addition of very small amounts of hydroquinones to prevent polymerization on storage.

Industrial production of acrylic resins is carried out under very carefully controlled conditions. The polymerization process is exothermic, and thus high pressure and high temperatures will be encountered. Acrylic resins may also be prepared by laboratory technicians at the time of need, such as in dentistry and surgery. In these cases two components are used, one being a liquid (the monomer), the second being a powder (the polymer as a powder with the presence of a catalyst and other ingredients). Mixing these two components leads to a dough-like material which can then be manipulated into the desired shape. Final hardening of the material can take place by heating or at room temperature, depending upon the formula used in the components. Heat-curing acrylic refers to materials requiring heat, and cold-curing, room temperature-curing, or self-curing refers to those acrylics requiring no heat. A typical self-curing acrylic may have the following formula: component A, methyl methacrylate monomer with 2% dimethyl *p*-toluidine (initiator); component B, polymerized methyl methacrylate in granular form and 2–3% benzoyl peroxide (activator). Combining these two components mixes the activator and initiator, bringing about polymerization of the monomer which, in turn, binds the powder particles together, forming a solid mass. Within 3–5 min the mass has hardened into its desired state. A residual quantity of monomer, generally less than 2%, remains in the final acrylic resins, whether heat-cured or self-cured.

Acute Toxicity

Table 1 summarizes the acute toxicity of a group of acrylic and methacrylic esters and shows at a glance the effect of structure on the activity being measured. One of the first detailed toxicological studies on the acrylic monomers was published by Deichmann in 1941 (*2*). His studies dealt with methyl, ethyl, and *n*-butyl methacrylates in rabbits, guinea pigs, and rats. Oral single doses of 7 ml/kg of methyl, 4–6 ml of ethyl, and 7–10 ml of butyl methacrylates were considered to be the minimum lethal doses for rabbits. Oral LD_{50} in rats was found to be 8.4 ml/kg for the methyl ester and 14.8 ml for the ethyl ester. The LD_{50} for the butyl ester could not be calculated, since doses higher than 20 ml/kg were not used, and at this dose only 2 out of 20 rats died.

Two other papers in the 1940's dealt with the

Table 1. Acute toxicity of acrylic and methacrylic esters. [a]

Compound	Acute oral LD_{50} (rats), g/kg	Skin toxicity LD_{50} (rabbit), ml/kg	Inhalation by rats: Concn, ppm	Time, hr	Mortality	Sat. vapor time for no deaths, hr
Methyl acrylate	0.2 (rabbit)	1.3	1000	4	3/6	
Ethyl acrylate	0.4 (rabbit)	1.95	4000	4	6/6	
	1.0		2000	4	5/6	
			1000	4	0/6	
			50000	0.25	6/6	
			540	19 days	12/18	
			70	30	2/29	
2-Hydroxy ethylacrylate	1.0	1.0	500	4	5/6	1
2-Ethoxy ethylacrylate	1.0	1.0	500	4	5/6	1
Ethoxy propylacrylate	0.8	1.4	250	4	1/6	1
n-Butyl acrylate	3.7	3.4	1000	4	5/6	0.5
2-Ethyl butylacrylate	6.5	5.5				4
2-Ethylhexyl acrylate	5.6	8.5				8
	6.4–12.8	>10 (guinea pig)				
Methyl methacrylate	8.4	>10	3750	8	ca. LC_{50}	
	6–7 (rabbit)		13500	3		
Ethyl methacrylate	14.8 (rat)					
	4–6 (rabbit)	>10	3300	8	ca. LC_{50}	
n-Butyl methacrylate	>20 (rat)	>10	>880	8		
	7–10 (rabbit)					
Isobutyl methacrylate	6.4–12.8 (rat)	>20 (guinea pig)	3600	6	0/3	
2-Ethyl isohexyl methacrylate	>12.8	>20 (guinea pig)	14	6	0/3	
2-Butyl octyl methacrylate	25.8					

[a] Data of Fassett (*1*).

toxicity of acrylic monomers. These included studies on the toxicity of methyl methacrylate by Spealman et al. in 1945 (*3*) and on the toxicity of methyl and ethyl acrylates by Treon and associates in 1949 (*4*).

Generally, the systemic toxic effects of the lower molecular weight acrylic monomers are manifested by an immediate increase in respiration followed by a decrease in 15–40 min. A prompt fall in blood pressure also occurs, followed by recovery within 4–5 min. As the animals aproach death, respiration becomes labored and irregular, lacrimation may occur, defecation and urination increase, and finally reflex activity ceases and the animals die in coma. Death in the past has been attributed to respiratory failure, but more recent evidence by Mir et al. (*5*) also implicates cardiac arrest.

The acrylic monomers are irritants to skin and mucous membranes. When placed in the eyes of animals they elicit a very severe response, and if not washed out can cause temporary or permanent damage. Methyl acrylate and methyl methacrylate can be absorbed through the skin, causing death of animals. For instance, the LD_{50} from dermal application of methyl acrylate has been reported to be 1.3 ml/kg (in rabbits), and greater than 10 ml/kg for methyl methacrylate (Table 1).

Inhalation studies on the acrylic monomers indicate that concentrations of 1000 ppm of methyl acrylate will kill 50% of exposed rats in 4 hr, while up to 4000 ppm of methyl methacrylate in an 8-hr exposure is required to produce a similar effect (Table 1). Inhalation toxicity has been reported for other acrylic monomers but, unfortunately, different methods of conducting the inhalation studies prevent quantitative comparisons of one monomer with the others. Spealman (*3*) noted in his studies that, by inhalation, methyl methacrylate was more acutely toxic for mice than acetone, but less toxic than ethyl acetate.

Surprisingly little research has been done on the metabolism of the acrylic monomers. Pantucek (*6*) suggests that methyl methacrylate may be oxidized completely, since no evidence of metabolites has been detected in the urine of animals exposed to the compound. He hypothesizes several biochemical pathways,

and concludes that because of the rapid rate of metabolism to compounds occurring naturally in body tissue, methyl methacrylate will have a low order of toxicity. The lack of biochemical studies of the other acrylic monomers prevents speculation on the fate of the other monomers in the series. As will be pointed out later, there is some indirect evidence to suggest that the acrylic esters behave biochemically in a different manner from the methacrylic esters.

There is some indication that the methacrylate esters can have an effect on "drug-metabolizing" enzymes. Lawrence and Autian (*7*) demonstrated that when animals were exposed to methyl methacrylate and ethyl methacrylate vapors, sleeping time (from administration of pentobarbital sodium) was extended. For example, exposure for 13 min to methyl methacrylate vapors increased the sleeping time in mice from approximately 90 min to 225 min. These studies, however, did not attempt to delineate whether this was the result of general enzyme inhibition (possibly from nonspecific hepatotoxicity), or whether it was due to a more selective enzymatic inhibition.

Subacute and Chronic Toxicity

Borzelleca and associates (*8*) studied the chronic oral toxicity of ethyl acrylate and methyl methacrylate. In one study, they administered levels of the monomer ranging from 6 to 2000 ppm to groups of rats for a period of 2 yr. The compounds were fed to the test animals in their drinking water.

Neither of the compounds at any of these doses produced a noticeable effect on mortality. At the highest dose level (2000 ppm) of ethyl acrylate, there was a definite decrease of weight in the female rats over the course of the study, and for the male rats in the first year. The authors observed a less pronounced effect with methyl methacrylate; depression of weight in both sexes was noted only in the first few weeks at the highest dose level. Hematologic effects and urine concentrations of protein and reducing agents did not differ significantly from control animals. Methyl methacrylate, at a level of 2000 ppm, did increase kidney-to-body weight ratios in the female rats. No effect was exhibited in the male rats. Other organ-to-body weight ratios were not significantly different from the controls (male and female) for either the acrylate or methacrylate monomers at any dose level. Gross and histopathologic examinations of tissues and organs did not reveal changes which could be attributed to the compounds studied.

In another study (*8*), the monomers were administered orally to dogs for a 2-yr period. The doses of ethyl acrylate administered were equivalent to 300–1000 ppm in the diet. Initially the animals could only tolerate doses of 300 ppm because of emesis. However, gradually the dose could be increased up to 1000 ppm by the end of the sixteenth week. Methyl methacrylate was administered in doses of 10–1000 ppm without subsequent emesis. The higher dose was eventually raised to 1500 ppm at the end of the ninth week. During the experimental period there was a slight decrease in weight of the animals at the highest dose level, but these values were not found to be significantly different from those for the controls. Under these experimental conditions, no real significant toxicity was observed which could be attributed to the acrylics studied.

Treon et al. (*4*) included in their published report a subacute toxicity study of orally administered methyl methacrylate to rabbits in a dose of approximately 1/10 (or 0.023 g/kg) of its LD_{50}. The animals received 24 doses over a 33-day period. Another group of rabbits received a dose of 0.0315 g/kg of ethyl acrylate, a total of 25 doses over a 35-day period. The authors concluded that the compounds had little toxic effect on the rabbits.

Treon and associates (*4*), in another study, repeatedly exposed animals (rats, rabbits, guinea pigs, and monkeys) to various concentrations of methyl and ethyl acrylate in air for periods of 7 hr. They recorded the concentration which did not kill any of the animals and the next higher concentration which did produce deaths. Their results are summarized in Table 2.

Subacute vapor toxicity has also been reported by Pozzani et al. (*9*) for ethyl acrylate. Rats were the experimental animal. The concentrations in air were adjusted to give values of 500, 250, and 62.5 ppm. Animals were exposed to these concentrations for seven hours at a time for up to 30 exposures. Deaths and other toxic effects were noted at the two highest concentrations, but little effect was found at the lowest concentration when compared to controls.

Table 2. Lethal and nonlethal concentrations of methyl and ethyl acrylates for various species.

Acrylate	Species	Concn producing no deaths, ppm	Concn producing deaths, ppm
Methyl acrylate	Rabbits and guinea pigs	95.1	237
	Rats	237	578
	Monkeys	31	—
Ethyl acrylate	Rabbits and guinea pigs	74.8	272
	Rats	272	501
	Monkeys	272	1204

Few published reports on subacute and chronic toxicities are available on the higher molecular weight acrylic monomers; thus, no judgment can be made about the toxic consequences of these monomers.

Structure–Toxicity Activity

Since the most widely used monomers of acrylic and methacrylic esters are those having low molecular weights such as the methyl and ethyl monomers, relatively little interest has been shown by toxicologists in studying the toxicity of many of the other acrylic or methacrylic esters. For this reason, until a few years ago, little toxicity data were available which could be subjected to rigorous mathematical analysis for structure–activity relationship. Several years ago the Materials Science Toxicology Laboratories undertook a series of studies on acrylic and methacrylic monomers to evaluate the effect of the structure on the biological response being measured. In one study, that dealing with LD_{50} determinations, a sufficient number of compounds were evaluated to permit a mathematical analysis on the resulting data (*10*). Several other studies were also conducted by the MST group on the effect of methacrylate monomers on the isolated rabbit heart (*5*), on isolated guinea pig ileum (*11*), on respiration and cardiovascular functions (*12*), and on developing embryo and fetus (*13*). These other studies, however, were not sufficiently encompassing to permit the use of mathematical models, although general trends of activity with structure were noted. In this section the studies alluded to above will be reviewed, with a subsequent mathematical analysis of the LD_{50}.

Isolated Heart Experiments

Mir et al. (*5*) studied the effect of twelve methacrylate esters and methacrylic acid on the isolated perfused rabbit heart. The compounds were dissolved in the perfusion fluid at concentrations of 1:1000, 1:10,000, and 1:100,000 (v/v). All of the compounds produced significant effects on the heart at one or more concentrations. The authors found that they could divide the compounds into three categories according to reversibility of heart response (Table 3). Methacrylic acid, methyl methacrylate, ethyl methacrylate, and dimethylaminoethyl methacrylate produced the harshest effect on the heart (irreversible effect at all three concentrations). Dimethylaminoethyl methacrylate was the most toxic compound in the series, producing cardiac standstill at a dilution of 1:10,000, while lauryl methacrylate showed the least depressant effect upon the isolated heart. Although it has been stated that respiratory failure is the cause of death in animals administered toxic levels of methacrylate esters, it seems that cardiac failure may also be a contributing factor. A clinical report, in fact, suggests that methyl methacrylate may have caused the deaths of patients during the use of acrylic bone cement (*14*).

The above authors ranked the compounds according to the effect on rate of contraction, force of contraction, and coronary flow and, in turn, compared these values to the LD_{50} values (IP, in mice, Table 4). Even though some of the most potent compounds (on the heart) were also the most toxic, and a number of the least

Table 3. Reversibility of heart response to methacrylates.[a]

	Group	Effect
I	Methacrylic acid Methyl methacrylate Ethyl methacrylate Dimethylaminoethyl methacrylate	Produced an irreversible effect on the isolated heart at all three concentrations
II	*n*-Propyl methacrylate *n*-Butyl methacrylate Isobutyl methacrylate Hydroxyethyl methacrylate *tert*-Butylaminoethyl methacrylate	Produced an irreversible effect on the isolated heart at the 1:1000 concentration but not at lower concentrations
III	1,3-Butylene dimethacrylate 2-Ethylhexyl methacrylate Isodecyl methacrylate Lauryl methacrylate	Produced a reversible effect on the isolated heart at all three concentrations

[a] Data of Mir et al. (*5*).

potent ones were also the least toxic, there were many other instances in which they did not follow the LD_{50} ranking.

Isolated Guinea Pig Ileum Experiments

In a second paper, Mir et al. (*11*) studied the same series of methacrylate esters as before in the isolated ileum system. Due to insufficient solubility in Tyrode's solution, three of the esters (isodecyl, 2-ethylhexyl, and lauryl methacrylates) were eliminated from the series. A fourth compound, 1,3-butylene dimethacrylate, was also eliminated from the series since it elicited a very slow response. Eight of the nine remaining compounds produced prompt and qualitatively uniform responses. Within 15–30 sec there was an inhibition of pendular movements and relaxation of the muscle. These compounds showed antagonism of the neurogenic and myogenic stimulant effects of acetylcholine and barium chloride upon the isolated ileum.

It was noted that the inhibitory effects for the eight compounds could be terminated by promptly washing the intestine with fresh Tyrode's solution.

Dimethylaminoethyl methacrylate gave an atypical response. This monomer elicted contraction of the isolated ileum, and was active in more dilute solutions than the others. Pretreatment of the ileum with atropine sulfate did not block or inhibit the contraction produced by the dimethylaminoethyl methacrylate, thus suggesting the effect was myogenic.

Respiration and Cardiovascular Function Experiments

Deichmann (*2*), as early as 1941, indicated that methyl, ethyl, and *n*-butyl methacrylates, when injected IV, caused a prompt and sudden fall in blood pressure, while respiration was stimulated immediately and remained at this level for up to 30 min. The final lethal dose, however, brought about respiratory failure although the hearts of these animals (rabbits) were still active.

Homsy et al. (*15*) also noted an immediate drop in blood pressure from administration of methyl methacrylate IV in dogs. Blood levels of 50–125 mg/100 ml were necessary to demonstrate a significant response. Homsy and associates were interested in methyl methacrylate because of its use in surgery as a bone cement.

Several clinical cases have also been reported which suggest that the methyl methacrylate in bone cement has led to a prompt drop in blood pressure, and at times, death (*14,16*). Generally, however, the drop was followed by a return to normal and few adverse effects developed. Charney, in his book (*17*) supports the safety of the acrylate cement in orthopedic surgery if prepared and used properly.

Because of the clinical implications from possible methyl methacrylate toxicity, Mir et al. (*12*) studied a series of methacrylic monomers as used in previous studies by this group (*2*). These investigators used dogs to study the

Table 4. Relative activity of methacrylates of equal dilutions.[a]

Compound (monomer)	Acute LD_{50} (IP, mice), ml/kg	Relative effect on isolated rabbit heart		
		Rate	Contraction	Coronary flow
Methacrylic acid	0.048	3 (−52.0%)	4 (−58.5%)	4 (−36.3%)
Dimethylaminoethyl methacrylate	0.104	1 (−73.0%)	1 (−84.9%)	1 (−67.5%)
tert-Butylaminoethyl methacrylate	0.190	9 (−12.6%)	11 (−17.9%)	9 (− 2.0%)
Hydroxyethyl methacrylate	0.497	5 (−24.5%)	7 (−40.8%)	+11 (+ 8.4%)[b]
n-Propyl methacrylate	1.121	10 (−12.3%)	6 (−42.6%)	7 (− 6.1%)
Methyl methacrylate	1.198	2 (−55.7%)	2 (−74.0%)	3 (−60.6%)
Isobutyl methacrylate	1.340	6 (−19.0%)	8 (−39.5%)	8 (− 4.2%)
Ethyl methacrylate	1.369	4 (−41.2%)	3 (−64.0%)	2 (−61.5%)
n-Butyl methacrylate	1.663	7 (−16.5%)	5 (−46.0%)	5 (−31.1%)
2-Ethylhexyl methacrylate	2.614	11 (− 8.3%)	10 (−20.3%)	+12 (+13.2%)[b]
1,3-Butylene dimethacrylate	3.598	8 (−13.3%)	9 (−35.8%)	6 (− 7.2%)
Isodecyl methacrylate	3.688	12 (− 6.3%)	12 (−13.2%)	+13 (+15.3%)[b]
Lauryl methacrylate	24.897	13 (− 3.6%)	13 (− 8.9%)	+10 (+ 5.5%)[b]

[a] Relative activity (ranking) determined by using the mean responses obtained at the three standard concentrations tested (1×10^{-3}, 10^{-4}, and 10^{-5} v/v). Data of Mir et al. (*5*).

[b] + indicates an increase over controls, with higher numbers indicating a greater increase.

effects of these monomers on blood pressure, heart rate, electrocardiogram, and respiration. The more soluble monomers were dissolved in normal saline, while the less soluble ones were prepared as suspensions in 0.1% gum acacia. Solutions and suspensions were prepared at a concentration of 5% (v/v).

From the blood pressure patterns observed, Mir was able to divide the compounds into three types: type I, compounds, including methacrylic acid, methyl, ethyl, *n*-propyl, *n*-butyl, isobutyl, and hydroxyethyl methacrylates, and 1,3-butylene dimethacrylate, producing a biphasic response (an abrupt fall, followed by a more sustained rise); type II, compounds including isodecyl, 2-ethylhexyl, lauryl, and *tert*-butylaminoethyl methacrylates, producing only a hypotensive response; type III, compounds producing a sustained hypertensive effect; only one compound, dimethylaminoethyl methacrylate, elicited this response. They noted that one of the compounds, dimethylaminoethyl methacrylate, produced bradycardia.

All of the compounds decreased heart rate within the dosage range studied; however, the magnitude of this change was much less than that noted for blood pressure. The compounds producing the greatest effect were propyl and isobutyl methacrylates, while lauryl and isodecyl methacrylates had the least effect.

The respiratory rate was increased by all the compounds, with butyl and isobutyl methacrylates exhibiting the most dramatic effect. Duration of action for most of the compounds was approximately twenty minutes, after which time respiration returned to normal.

Results from the electrocardiograms were more complex, but Mir was also able to divide the compounds into three types, as mentioned above. Details of these results are discussed in the original paper.

Powell et al. (*14*) has suggested that methyl methacrylate may elicit hypotensive effects due to vasodilatory action. Results of the isolated ileum experiments reviewed earlier showing that most of the methacrylates relax smooth muscle lend support to Powell's thesis.

Embryonic-Fetal Toxicity and Teratogenic Experiments

The effects of five methacrylic esters and acrylic acid upon the developing embryo and fetus in rats have been studied by Singh et al. (*13*). Intraperitoneal injections were administered to pregnant rats on days 5, 10, and 15 of gestation. Three dose levels were employed based upon the LD_{50}. Several control groups were also included in the study, consisting of an untreated group and groups treated with distilled water, normal saline, and cottonseed oil. The dose of these "treated" controls was 0.82 ml/kg or the largest volume administered in the treated animals. On day 20 of gestation, one day before expected parturition, all the animals were sacrificed by ether inhalation. The uterine horns and ovaries were exposed, examined, and the results recorded. Table 5 presents the data of Singh et al. and indicates the number of corpora lutea, number of resorptions, dead fetuses, live fetuses, and mean weights of fetuses. Gross and skeletal malformations were also recorded (Table 6).

Under these experimental conditions, all of the methacrylate esters included in the study produced deleterious effects upon the developing embryo and fetus. The effects were compound and generally dose-related. Isodecyl methacrylate had a high incidence of resorption (44% for the highest dose level), suggesting a potent early embryotoxic effect (Table 5). Fetal sizes were smaller, on the whole, in the methacrylate-treated groups than the pooled treated control groups. The greatest number of malformations occurred in the animals receiving the high doses of methyl and ethyl methacrylates (Table 6). Sufficient numbers of monomers were not included in the study to assess in detail the structure-toxicity effects of these compounds. It should be pointed out that cottonseed oil had an effect on fetal size and produced skeletal abnormalities comparable to those found in the test animals receiving the monomers.

Structure–Activity Relationship

Various mathematical models can be used to relate the structure of compounds to specific biological activity. By use of these models, it is often possible to predict the biological activity of a new compound in the same or similar series of compounds for which toxicological data are available. Lawrence and associates (*10*) utilized two mathematical models in one of their studies on the toxicity of acrylic and

Table 5. Gross and skeletal malformations produced by methacrylate esters.[a]

Treatment group	Volume injected, ml/kg	No. (%) of resorptions[b]	No. (%) of gross abnormalities[c]	No. (%) of skeletal abnormalities[d]
Untreated controls	—	0	0	0
Distilled water	0.8222	3 (7.7)	0	1 (5.0)
Normal saline	0.8222	4 (7.4)	1 (2.0)	2 (7.7)
Cottonseed oil	0.8222	0	1 (2.0)	4 (15.4)
Methyl methacrylate	0.4427	3 (5.9)	8 (16.7)*	0
	0.2656	3 (5.7)	4 (8.0)*	0
	0.1328	2 (4.4)	1 (2.3)	0
Ethyl methacrylate	0.4076	7 (12.1)*	8 (15.7)*	3 (11.1)
	0.2446	6 (12.5)*	5 (11.9)*	2 (7.7)
	0.1223	5 (9.4)*	3 (6.3)*	1 (5.0)
n-Butyl methacrylate	0.7680	18 (34.6)*	4 (11.8)*	2 (10.5)
	0.4608	3 (5.2)	2 (3.6)*	2 (6.7)
	0.2304	1 (2.0)	2 (4.2)*	2 (7.7)
Isobutyl methacrylate	0.4666	9 (16.4)*	5 (10.9)*	2 (8.0)
	0.2799	2 (4.0)	3 (6.3)*	2 (7.7)
	0.1400	4 (8.2)	3 (6.7)*	0
Isodecyl methacrylate	0.8222	19 (44.2)*	1 (4.2)*	2 (13.3)
	0.4933	14 (25.0)*	1 (2.5)	1 (4.3)
	0.2467	3 (5.1)	1 (1.8)	0
Acrylic acid	0.0075	3 (6.0)	4 (9.1)*	4 (16.7)*
	0.0045	2 (3.6)	2 (3.7)*	3 (10.7)
	0.0023	0	0	3 (9.7)

[a] Data of Singh et al. (*13*).
[b] Percentage resorptions based on total number of resorptions, dead and live fetuses.
[c] Percentage gross abnormalities are based on total number of fetuses.
[d] Percentage skeletal abnormalities are based on total number of stained fetuses (~50% of total fetuses).
* Values greater than the 95% confidence interval of the pooled volume control.

Table 6. Embryonic-fetal toxicity of a group of methacrylate esters on rat fetuses.[a]

Treatment group	Volume injected, ml/kg[b]	No. of corpora lutea	No. (%) of resorptions	No. (%) of dead fetuses	No. (%) of live fetuses	Mean weight of fetuses, g[c]
Untreated controls	—	60	0	0	59 (100)	4.83±0.01
Distilled water	0.8222	53	3 (7.7)	0	36 (92.3)	3.82±0.12[d]
Normal saline	0.8222	60	4 (7.4)	0	50 (92.6)	4.15±0.11[d]
Cottonseed oil	0.8222	53	0	0	50 (100)	3.85±0.08[d]
Methyl methacrylate	0.4427	51	3 (5.9)	0	48 (94.1)	4.17±0.05[d]
	0.2656	54	3 (5.7)	0	50 (94.3)	4.22±0.06[d]
	0.1328	53	2 (4.4)	0	43 (95.6)	4.22±0.12[d]
Ethyl methacrylate	0.4076	58	7 (12.1)	0	51 (87.9)	3.80±0.08[d]
	0.2446	53	6 (12.5)	0	42 (87.5)	3.30±0.37[d]
	0.1223	53	5 (9.4)	0	48 (90.6)	4.26±0.36
n-Butyl methacrylate	0.7680	54	18 (34.6)	0	34 (65.4)	3.86±0.20[d]
	0.4608	58	3 (5.2)	0	55 (94.8)	3.95±0.12[d]
	0.2304	55	1 (2.0)	0	48 (98.0)	3.98±0.12[d]
Isobutyl methacrylate	0.4666	55	9 (16.4)	0	46 (83.6)	4.08±0.16[d]
	0.2799	52	2 (4.0)	0	48 (96.0)	4.01±0.06[d]
	0.1400	51	4 (8.2)	0	45 (91.8)	3.89±0.08[d]
Isodecyl methacrylate	0.8222	54	19 (44.2)	0	24 (55.8)*	3.42±0.20[d]
	0.4933	57	14 (25.0)	2 (3.6)	40 (71.4)	3.13±0.21[d]
	0.2467	60	3 (5.1)	0	56 (94.9)	4.09±0.08[d]
Acrylic acid	0.0075	52	3 (6.0)	3 (6)	44 (88.0)	3.80±0.34[d]
	0.0045	56	2 (3.6)	0	54 (96.4)	3.96±0.11[d]
	0.0023	57	0	0	57 (100)	4.09±0.08[d]

[a] Data of Singh et al. (*13*).
[b] Five pregnant female rats were injected in each group on days 5, 10, and 15 of pregnancy.
[c] Average values ± the standard error of the mean for each group.
[d] Significantly different from untreated controls ($p \leq 0.01$).
* One rat aborted all ten fetuses.

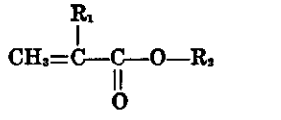
methacrylic esters in mice. These authors used experimentally determined LD_{50} values (Table 7) of the monomers as the specific toxicogenic parameter in the mathematical models. The two models used by the authors were the Free-Wilson model and the Hansch model. Both of these models assume a common mode of biologic activity for all molecules of the series.

The Free-Wilson model can be depicted as:

Biologic activity = overall average + contribution of segment 1 + segment 2 + segment N

It is assumed that for an analogous series of compounds, the observed biological response is the sum of mutually independent contributions from the various segments of the molecule. For a series of related compounds the biological activity of each segment can be calculated by the use of linear equations.

In the series of compounds studied, the segments R_1 and R_2 are shown in structure I.



I

It is evident that, when R_1 = H, a series of acrylic esters results, and when R_1 = CH_3, a series of methacrylic esters is formed. From the LD_{50} data shown in Table 7 and by use of the Free-Wilson model, the activity of each segment was found (Table 8). The higher the numerical value, the greater is the contribution of the segment to the total toxicity. On the other hand, when the numerical values are negative, this indicates that the substituent is reducing the toxicity. The Free-Wilson model, therefore, permits (for these series of compounds) a quantitative ranking of the toxicity of substituents at a given segment.

Table 7. LD_{50} values in mice for a series of esters of acrylic and methacrylic acids.[a]

No.	Compound	Acute IP	
		LD_{50}, ml/kg	LD_{50}, mole/10^6 g
1	Glacial acrylic acid	0.016	0.225
2	Methyl acrylate	0.265	2.949
3	Ethyl acrylate	0.648	5.986
4	Butyl acrylate	0.926	6.653
5	Isobutyl acrylate	0.854	5.932
6	2-Ethylhexyl acrylate	1.506	7.195
7	Glacial methacrylic acid	0.048	0.564
8	Methyl methacrylate	1.198	11.217
9	Ethyl methacrylate	1.369	10.896
10	Butyl methacrylate	1.663	10.481
11	Isobutyl methacrylate	1.340	8.398
12	Isodecyl methacrylate	3.688	14.251
13	Lauryl methacrylate	24.897	84.531
14	*tert*-Butylaminoethyl methacrylate	0.190	0.937
15	Dimethylaminoethyl methacrylate	0.104	0.618
16	Hydoxyethyl methacrylate	0.497	4.060
17	1,3-Butylene dimethacrylate	3.598	16.063
18	Trimethylolpropane trimethacrylate	2.727	8.537

[a] Data of Lawrence et al. (*10*).

The Hansch model can be represented in a general manner:

$$-\log(\text{biologic response}) = a\pi^2 + b\pi + c\sigma + d$$

where π is the logarithm of the octanol–water partition coefficient, and σ is the Hammett or Taft substituent constant for the compound under study. For a series of related compounds in which a specific biologic response is known (e.g., LD_{50}), corresponding equations can be solved for the coefficients a, b, c, and d. The term π can be considered a measure of the transport and hydrophobic bonding tendencies of the compound. The Hammett or Taft value is related to the electronic distribution within the molecule.

For the acrylic toxicity studies, Lawrence et al. (*10*) used the Hansch equation:

$$\log(1.0/LD_{50}) = a\pi^2 + b\pi cQ^{\sigma}(C) + d$$

The term $Q^{\sigma}(C)$ is related to the net charge on the carbonyl carbon and may be calculated by the use of suitable equations. For the series of compounds in Table 7, the partition coefficients were obtained from the literature or calculated. By the use of multiple regression analyses, various combinations of π^2, π, $Q^{\sigma}(C)$, and various subseries of compounds, it was possible to discern the importance of π and its influence upon the toxicity of the compound. For example, when the 18 molecules shown in Table 7 were considered, 52% of the variance in toxicity could be related to the use of the single parameter π. This implies that the transport of these molecules or their hydrophobic properties are probably important in eliciting toxic effects. In the same series, the charge on the carbonyl carbon [$Q^{\sigma}(C)$] accounted for approximately 43% of the toxicity

Table 8. Structure–activity analyses for acrylate–methacrylate series by use of Free-Wilson model.[a]

Segment	$CH_2=CR_1COOR_2$ substituent	Substituent contributions, −log (LD_{50}) Units		
		All[b]	All but Bu[c]	All but Bu, NH_2, OH[d]
R_1	H	0.2120	0.2249	0.2001
	CH_3	−0.1060	−0.1229	−0.1493
R_2	H	1.0846	1.0671	1.2100
	$CH_2CH_2N(CH_3)_2$	1.0051	1.0026	—
	$CH_2CH_2NHC(CH_3)_3$	0.8241	0.8216	—
	CH_2CH_2OH	0.1881	0.1856	—
	CH_3	−0.1229	−0.1404	−0.0032
	$CH_2C(CH_3)=C(CH_3)-COOCH_2)_2C_2H_5$	−0.1349	−0.1374	−0.0062
	$CH_2CH(CH_3)_2$	−0.2114	−0.2289	−0.0853
	C_2H_5	−0.2714	−0.2895	−0.1453
	C_4H_9	−0.2844	−0.3773	−0.2352
	$(CH_2)_7CH(CH_3)_2$	−0.3539	−0.3564	−0.2128
	$CH_2CH(C_2H_5)CH_2CH_2CH_3$	−0.3789	−0.4125	−0.2677
	$CH_2CH_2CH(CH_3)OOCC(CH_3)=CH_2$	−0.4139	−0.4164	−0.2728
	$(CH_2)_{11}CH_3$	−1.1239	−1.1264	−0.9828
Average log $1/LD_{50}$, μ[e]		−0.6901	−0.6706	−0.7879

[a] Data of Lawrence et al. (*10*).
[b] Calculations based on all of the 18 compounds listed in Table 7.
[c] Calculations based on all of the compounds listed in Table 7 except butyl methacrylate.
[d] Calculations based on all of the compounds in Table 7 except butyl methacrylate and molecules in which R_2 contains an amine or hydroxyl group.
[e] $-\log(LD_{50}) = \mu + \sum$ substituent contributions

variation. When π and charge were taken together, up to 67% of the variance could be explained. A high correlation of structure–toxicity activity was found when the Hansch analyses were conducted using only the data from the acrylic series. The methacrylic series contains (at R_2) some compounds with amine or hydroxyl groups (Table 7). When these compounds were eliminated from the methacrylic series, a very high correlation resulted.

Interpretation of the results from the Free-Wilson and Hansch models suggests that the compounds in the acrylic acid series are possibly undergoing hydrolysis, leading to the very toxic acrylic acid, while the toxicity for the methacrylic series may be more dependent on the intact molecule. Also, it seems apparent that when functional groups such as hydroxyl or amine groups are contained at R_2, the mechanism of toxicity is different from the remaining compounds in the methacrylic series.

Although the Free-Wilson model did serve a useful purpose in ranking the toxicity of segments of the test compounds, its ability to predict the LD_{50} of an untested compound in the series was poor. On the other hand, the Hansch model provided reasonable predictions for the LD_{50} of several other compounds in the series not previously tested. For instance, the predicted LD_{50} of butyl methacrylate was 0.01197 mole/kg, while the experimentally determined value was 0.01048 mole/kg. In another report, Bass et al. (*18*) predicted the LD_{50} for four acrylic esters and four methacrylic esters. The agreement between the predicted and the actual values were, in general, good.

The generation of predictive toxicologic values, such as LD_{50}, by mathematical models by using a series of closely related compounds (as the acrylic or methacrylic series) can be quite helpful to an investigator in discerning whether or not one or more members of the series exerts its toxic effect through a different mechanism than the other members of the series. In addition, these investigators (*13,18*) demonstrated the usefulness of this approach in predicting the toxicity of new or untested compounds within the series.

Potential Health Threats

As this paper indicates, much of the toxicity data for the acrylic and methacrylic monomers center on the lower molecular weight esters. Considerably fewer toxicologic data have been generated on the higher molecular weight esters and those compounds having other functional groups such as hydroxyl and amine groups. This perhaps is understandable, since production of the other monomers is not as great, and their applications are quite limited. Chronic toxicity studies on the lower molecular weight esters are not extensive, but data which have been generated supports the contention that these have a very low order of toxicity, even at doses or concentrations many times greater than would be envisioned in a working environment. Industrial experiences with these monomers has led to the same general conclusion. Threshold limit values (TLV) are 100 ppm for methyl methacrylate and 25 ppm for ethyl acrylate.

Obviously, caution should still prevail in an industrial environment where the acrylic and methacrylic monomers are manufactured or used, since they are sufficiently irritating that they may lead to occupational injuries. For certain workers, inhalation of the monomer may lead to respiratory problems which can necessitate lost working time. The potential sensitizing activity of the esters also warrants exclusion of workers susceptible to allergic episodes from an environment in which the monomers will be contacted. Since preliminary toxicity data in animals indicate that the monomers may have an effect on the drug-metabolizing enzymes, workers who are on maintenance drug therapy might respond differently to the drug than the physician anticipates. How important this type of adverse drug effect might be clinically is not presently known.

Because the monomers do affect blood pressure, respiration, and the heart, workers predisposed to cardiovascular disease might be considered a high-risk group and, thus, special precautions should be taken to guard these persons from excessive exposure to the esters.

Exposure of pregnant women to a working environment containing these esters is always a potential health threat, since these monomers have been found to act as embryotoxic and teratogenic agents. Comparison of doses used in animal studies which inflicted fetal harm to concentrations of the monomers which would be absorbed by a worker in a normal industrial environment indicates that embryotoxic and teratogenic episodes would occur rarely, if at all.

The apparent rapid metabolism and elimination of the lower molecular weight esters suggests that these monomers should not produce a cumulative toxic effect. Both animal experiments and long-term monitoring of workers in industrial environments demonstrate that these agents are not carcinogenic.

A problem which will hopefully receive more attention in the near future is the exposure of laboratory workers, medical personnel, and even patients to monomers which are used to prepare various dental restorative materials and orthopedic cement, since the standards for occupational hygiene and safety in many of these environments are not at the same level as they are in an industrial environment.

An important point needs to be emphasized pertinent to other esters falling into the acrylic and methacrylic series, in particular agents which have functional groups other than simple alkyl constituents. The toxic mechanisms of these may not be the same as those of the lower molecular weight esters. Indeed, as this paper has pointed out, there is evidence suggestive of a marked difference in action of esters having hydroxyl and amino groups, and thus these compounds may present toxicological risks not originally anticipated. Since these other monomers have not been studied in extensive subacute or chronic animal experiments, they still present an unknown risk to the working environment. Should any of these monomers find greater use, there will certainly be an urgent need to develop sound chronic toxicologic profiles for them.

As far as is known, the acrylic monomers as a whole have not presented an environmental health problem when they are deposited into streams and water bodies. Whether this lack of harm is due to the relatively small amounts deposited, or to the rapid conversion to biologically compatible components is unknown.

Judging from current information, acrylic and methacrylic esters appear to present no undue toxicologic threat to workers in industrial firms having acceptable standards of hygiene. Laboratory workers, conversely, may

indeed become a high risk group if caution is not taken to reduce the exposure of these persons to the monomers. The production of new esters or the expansion of production of those esters having other functional groups should be preceded by adequate subacute and chronic toxicity studies to aid in defining the risk they present.

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